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THE MANNER IN WHICH FOOD CONTROLS THE BULK OF THE FECES *

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EVERYONE is fully aware that the causes of constipation are numerous. It is often very difficult to determine the relative importance of each factor. There are many normal people who, although consuming very concentrated, highly purified, non residue diets, are nevertheless rarely constipated. Others there are who in spite of using all possible dietary aids are not able to have a daily evacuation of the bowels. So there is considerable doubt in our minds as to whether food is the main factor in determining the regularity of stool evacuation. Furthermore, there is abundant room for argument as to whether or not a daily evacuation is necessary for the maintenance of sound health.

One need not be concerned with the causes or clinical import of constipation to be able to prove that in a given normal individual one can markedly affect the stool volume by dietary means.

In this paper we wish to present the experimental results accumulated from time to time over the past several years by using as experimental subjects medical students who trained themselves to a regular time for stool evacuation. It is our conviction that results in this field are much more convincing and applicable if the human subject is used as the experimental animal. With these normal individuals we propose to show the effects of food on the volume of the stool. We shall then explain partially at least the results found.

EFFECTS OF DIGESTIBLE PROTEIN, FAT AND CARBOHYDRATE

Both clinicians and physiologists agree that the indigestible carbohydrates of foods have a greater effect on stool volume than the digestible and absorbable protein, fat and carbohydrate. Nevertheless, one can easily

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show the effect of carbohydrate even in the case of non residue diets on the volume of the stool. In table 1 are recorded the results of an experiment carried out in 1929 [1] on three students. It can be seen that when there was a predominance of carbohydrate in the diet, the stool volumes exceeded those found in the periods of either high protein or high fat feeding. When much protein was fed, the small stool volume is very evident. Although all three subjects' stool volumes increased on high carbohydrate diets, there are differences in the individual responses. This illustrates the difference found among normal individuals.

The explanation of the different effects of protein, fat and carbohydrate on the stool volume lies in the fact that even in case of non residue diets

TABLE I

Influence of Digestible Protein, Fat and Carbohydrate on the Volume of the Stool

Diet 7-day Periods	Protein	Fat	Starch	Sugar	Average 24-hr. Volume of Stool		
					Subjects		
					K	McC	M
	gm.	gm.	gm.	gm.	gm.	gm.	gm.
High protein	250	70–100	55–70	30–40	83	55	180
High sugar	50	100	135	365	222	205	329
High starch	50	100	400	100	193	121	253
High fat	50	300	75	25	126	118	211

which are from 90 to 95 per cent digested and absorbed, there is, nevertheless, a residue which reaches the bacteria-infested large intestine. The diet determines the character of this residue. That even small amounts of sucrose reach the colon is probable because of its relatively slower absorption rate [2] as compared to glucose and galactose. The putrefactive products of protein are probably, taken as a whole, costive in their effects. On the other hand the products of carbohydrate fermentation are the lower volatile fatty acids, lactic acid and carbon dioxide, which are definitely proved to be laxative.[3] Furthermore, it must be remembered, as emphasized by Kendall,[4] that bacteria will break down sugar in preference to protein for their energy needs. Thus, in the intestine just as in culture media, as long as food residues contain a certain amount of sugar, protein breakdown (putrefaction) is spared, i.e., reduced to a minimum. Thus a high carbohydrate diet has at least two effects:

(*a*) The products of sugar fermentation are laxative.

(*b*) The presence of sugar spares the breakdown of protein and thus minimizes the formation of costive products of putrefaction.

Table 2 shows that the volatile fatty acids in stools of normal men are increased by high carbohydrate diets, and that the amounts of volatile fatty acids increase with the rise in stool volume. Pediatricians [5] have long recognized the laxative nature of these acids and that their increased output accompanies sugar feedings to infants.

Lactic acid appears in cultures of almost all types of bacteria as long as there is abundance of sugar in the media. Pittman and Olmsted [6] could not demonstrate lactic acid in human stools. We interpret this finding as evidence of the remarkable symbiotic action of the many types of bacteria found in the intestine. Lactic acid incubated in raw fecal matter disappears.

Carbon dioxide and hydrogen are produced in largest quantities when sugar predominates in the diet. Physicians should realize that these gases are normal excretory products of bacterial fermentation. Many people and some physicians look upon the passage of flatus as an abnormal condition, whereas it is as normal as the passage of feces.

TABLE II

Effect of Diet (Non-Residue) on Total Volatile Fatty Acid Excretion

Diet	Average c.c. 0.1 N. acid in 24 hours		
	Subjects		
	K	McC	M
	c.c.	c.c.	c.c.
High protein	90	71	179
High sugar	148	278	447
High starch	125	191	349
High fat	82	129	221

THE INDIGESTIBLE CARBOHYDRATES

When the physician is called upon to prescribe a diet as an adjunct in the treatment of constipation, he instructs his patient to take a "bulky" diet. He means by this that the diet should be rich in vegetables, fruits, and the bran of cereals. These foods contain indigestible carbohydrates which are supposed to pass through the upper intestinal tract unchanged and thus add to the bulk of the feces. The present conception of the action of bulky foods can be expressed by a quotation from Starling's "Textbook of Physiology" [7] (p. 597). "The indigestible cellulose in the food is not without value. It has been shown previously that the peristaltic contractions of the intestine are roused primarily by the mechanical stimulus of distention. If the food is capable of entire digestion and absorption, the amount of feces formed is limited to that produced by the intestinal wall itself. The small bulk exercises very little stimulating effect on the intestine, and the

movements of the latter will therefore tend to be sluggish, especially in the absence of the mechanical stimulus determined by physical exercise. The presence of a certain amount of cellulose in the diet may therefore be of considerable advantage by giving bulk to the feces and ensuring the proper regular evacuation of the lower gut. It is probable that the constipation which is so common a disorder in civilized communities is due as much to the refinement in the preparation of food as to the prevalence of sedentary occupations incident on the working of such communities." The current belief, therefore, emphasizes the mechanical distention of the colon by bulky foods as the stimulus which prompts evacuation. The results of the experiments we are about to show suggest another important factor in addition to the mechanical one.

The indigestible portion of carbohydrate foods consists of the structural material of plants. Chemically it can be divided into three groups: cellulose, lignin, and hemicellulose. Cellulose is a polysaccharide which can be converted into glucose. It is insoluble in water, cannot be broken up by any of the enzymes of the mammalian intestinal tract, but can be broken down to glucose by the hydrolytic action of concentrated mineral acids. Lignin is an incrustation associated closely with cellulose and found in the harder portions of the structural parts of plants, especially in wood. The cellulose-lignin combination is dissociated by chlorine, sulphite solutions, strong alkalis and mineral acids. Lignin is not a carbohydrate. The hemicelluloses are a group of polysaccharides, soluble in dilute alkalis and for the greater part convertible into simple sugars by dilute acid hydrolysis. The sugars making up the major portion of various hemicelluloses are the pentoses (five carbon sugars), galactose, levulose and mannose. Although neither lignin, cellulose nor hemicellulose can be digested, nevertheless they all can be attacked by bacteria. If this were not so, our farm animals grazing on pastures would have great difficulty in maintaining their nutrition. In the intestinal tracts of herbivora bacteria convert cellulose and the hemicelluloses to much the same products as they do in the case of the soluble sugars and starches. It has been estimated that the grazing animal obtains as much as 25 per cent of his calories from the absorption of the fatty acids which bacteria produce by the fermentation of cellulose and hemicelluloses. Pringsheim [8] has discussed this matter fully. These well known facts raise several very pertinent questions: Are cellulose and hemicelluloses broken down in the same fashion in the intestinal tract of man, and, if so, is the action of bulky foods mechanical or chemical? If bacteria do break down cellulose and hemicellulose to soluble products, how can their effect be a mechanical one? To what extent are cellulose, lignin and hemicelluloses broken down by bacteria in the intestinal tract of man? The literature does not contain satisfactory answers to these questions,[9] because of the absence of satisfactory methods for determining quantitatively cellulose, lignin and the hemicelluloses.

If one studies an analysis of any cereal food product, he finds listed: protein, fat, starch, ash, moisture and crude fiber. Crude fiber is the term used by analytical food chemists to denote the indigestible fraction of foods. The method for determining crude fiber goes back seventy years. It originated in the little town of Weende, Germany, and is known also as the Weende method. This procedure makes use of a double digestion, first with weak acid and second with weak alkali. Between each digestion the soluble products are filtered off and discarded. The crude fiber is what remains after these digestions. Chemists have long known that crude fiber represented merely an unknown fraction, varying with each material analyzed, of the combined cellulose, lignin and hemicellulose. Because the crude fiber method was completely unsatisfactory as a means of studying the amounts of indigestible residue in foods and feces, Williams and Olmsted [10] published a biochemical method for the quantitative determination of each constituent of indigestible residue. It gave us the opportunity of conducting an experiment to determine the true action of bulky foods.

This experiment [11] was conducted with medical students. The materials fed were indigestible residues isolated from widely varying sources, concentrated by simple means which carefully preserved their essential chemical composition. Table 3 shows that 50 to 80 per cent of these

TABLE III

Analysis of Materials Fed

Materials added to basal diet	Wheat bran	Alfalfa leaf meal	Carrots	Corn germ meal	Cotton seed hull meal	Sugar beet pulp	Canned peas	Cabbage	Agar agar	Cellu flour
	%	%	%	%	%	%	%	%	%	%
Cellulose	16.9	32.5	23.2	15.8	19.4	34.2	35.0	29.5	0.0	78.8
Lignin	7.8	15.0	3.4	2.4	20.8	2.5	1.7	2.6	0.0	0.0
Hemicellulose	35.2	19.2	28.8	30.8	31.5	29.2	10.9	28.3	81.0	16.9
Starch, protein, ash, moisture and fat	35.7	32.7	40.6	49.7	17.5	30.3	49.5	37.1	8.5	3.1
Total	95.6	99.4	96.0	98.7	99.2	96.2	97.1	97.5	99.5	98.8

residues consisted of cellulose, lignin and hemicellulose, but that no two of these residues had the same composition. This affords opportunity for studying the relative effects of cellulose, hemicellulose and lignin. Before our experiment we did not know which of these three components was most important. We, therefore, maintained the amount of cellulose plus lignin constant (10 gm. per day) and let the amount of hemicellulose be variable. To a basal diet of non-residue foods each residue was added for a period of six days. The stools were analyzed for volatile fatty acids, cellulose, lignin, hemicellulose and reducing sugars.

Criteria of Laxative Action

Obviously a material is not laxative merely because it increases the stool weight. If this were not so, inert materials recoverable 100 per cent in the feces would be considered laxative. We have found that certain materials of vegetable origin classed as roughage are almost completely recovered in the stools, do add to the weight of a basal stool but are quite constipating whether judged subjectively or by trauma to the colon. We adopted two criteria: (1) The impression of the subject as to whether or not the bowel movement was satisfactory. (2) The weight of feces over and above the weight of the residue recovered in the feces. For instance, if 70 gm. of substance *A* were fed, 65 gm. recovered in the feces and the weight of feces increased only 90 gm., this material could not be considered laxative. If, on the other hand, 100 gm. substance *B* were fed, 29 gm. recovered in the feces and the weight of feces increased 550 gm., this substance would be considered laxative.

As an index of true increase in stool weight we adopted a factor, termed "Increment in Stool Weight," which is obtained by subtracting from the stool weight of a residue feeding period the weight of residue passing the gut and the weight of a basal (residue free) period stool. This increment represents either increased free fluid content or water absorbed by the residue remaining in the stool.

Results

Table 4 shows the increment in stool weights for seven days after these residues had been fed for six days. Basal stool weights were markedly increased in the cases of bran, carrots, corn germ meal, cabbage, agar and sugar beet pulp. Poor subjective results with only slight increment in stool

Table IV

Relative Effectiveness of Materials Fed

Materials Added to Basal Diet	Weight of Residue Fed	Increment in Stool Weight				Ratio: Increment to Residue Fed
		Subject F	Subject W	Subject H	Average of F, W and H	
	gm.	gm.	gm.	gm.	gm.	
Cellu flour	71.7	223	119	(−) 63	93	1.34
Cotton seed hull	105.9	104	123	66	97	0.91
Canned peas	74.5	114	255	134	167	2.24
Alfalfa leaf	79.5	182	318	221	240	3.04
Sugar beet pulp	93.4	662	372	171	401	4.29
Wheat bran	146.0	575	578	373	475	3.25
Carrots	106.8	700	589	336	541	5.06
Corn germ meal	154.4	590	563	581	578	3.74
Cabbage	101.5	647	781	449	625	6.15
Agar agar	80.2	835	719	445	666	8.30

weights are noted in the cases of cellu flour, peas, cotton seed hull and alfalfa leaf. These results take on significance when we compare the relative increases in stool weights with the chemical analyses of the residues. Table 3 shows these analyses. The cellulose varies in most of the materials between zero and 35 per cent; lignin between zero and 21 per cent; and hemicellulose between 10 and 35 per cent. In table 5 the characteristics of the chemical composition are stated very simply. Each material, which when fed resulted in a substantial increment of stool weight (essentially doubling of basal stool weight), is boxed.

TABLE V

Classification of Residues on the Bases of the Increase of Stool Volume and Their Chemical Composition

High in cellulose	Alfalfa leaf, **beet pulp**, peas **cabbage** and cellu.
High in lignin	Alfalfa leaf, cotton seed hull.
High in hemicellulose	**Bran**, **carrots**, **corn germ meal**, Cotton seed hull, **beet pulp**, **Cabbage** **agar**.

A glance leaves not much doubt that when hemicellulose is high, the residue is apt to be laxative. Seven of these 10 materials fed proved on analysis to contain 30 per cent or more hemicellulose. Of these seven, six, when fed, resulted in a marked increment of stool weight.

Two materials contained 15 to 20 per cent lignin, the remaining materials contained only 1 to 3 per cent lignin. Alfalfa leaf and cotton seed hull, when fed, resulted in stool weights very little above the basal level.

Five of these residues were high in cellulose. That is, the analyses showed at least 30 per cent cellulose. Of these five, only two (cabbage and sugar beet pulp) resulted in marked increment of stool weight. Cellu flour was 79 per cent cellulose and when it was fed, the stools were of low weight. If cellulose were stimulating because of its mechanical bulk, one would expect cellu flour to be highly stimulating, but such is not the case.

From this analysis, we conclude that the comparison of these materials shows that when hemicelluloses predominate in the residue, the stool weights increase definitely; when lignin is present, in percentages as high as 20, the stools are increased above the basal level only to the extent of the material fed. Cotton seed hull was over 30 per cent hemicellulose. This level in other materials resulted in marked increase of stool weight but the 20 per

cent lignin present in cotton seed hulls apparently counteracted the effect of hemicelluloses. The explanation will be considered below.

Disappearance of Indigestible Residues

The analysis of the stools for lignin, cellulose and hemicellulose revealed a remarkably high percentage of disappearance of these substances during their passage through the human gut. Table 6 summarizes the disappear-

Table VI

Disappearance of Lignin, Cellulose and Hemicellulose

Residue Added to Basal Diet	Fractions of Indigestible Residue						Total Residue	
	Lignin		Cellulose		Hemicellulose			
	gm.	%	gm.	%	gm.	%	gm.	%
Wheat bran	1.9	10	11.4	30	29.8	35	43.1	30
Corn germ meal	*	*	29.5	57	59.5	63	89.0	60
Carrots	*	*	34.5	67	39.5	85	74.4	74
Cotton seed hull	3.7	12	4.8	14	10.6	30	19.1	18
Cabbage	*	*	29.8	55	33.1	80	62.9	80
Sugar beet pulp	*	*	30.9	55	29.7	89	60.6	65
Alfalfa leaf meal	0.6	3	5.0	12	1.1	6	6.7	9
Canned peas	*	*	25.4	45	12.1	84	37.5	53
Agar agar	—	—	—	—	48.6	60	48.6	60
Cellu flour	—	—	4.2	7	3.2	29	7.4	10

* Lignin content too small for valid results.

ance of each material fed. Lignin was present in bran, cotton seed hull and alfalfa leaf in a considerable quantity. The stools passed during the feeding of these substances contained 88 to 97 per cent of the amounts fed. The lignin present in the other substances fed was so small that the high percentage disappearance, in our opinion, is of no significance. Lignin then is very resistant to bacterial attack. Cellulose disappeared to the extent of 7 per cent in the case of cellu flour, up to 67 per cent in the case of carrots. In six of the materials fed more than 45 per cent of the cellulose was lost during its passage through the intestinal tract. Apparently bacteria have little difficulty in attacking the hemicelluloses for they disappeared to a greater extent than either lignin or cellulose. In six of the 10 materials fed the total loss in this fraction was over 60 per cent. In the case of carrots, cabbage, beet pulp and peas over 80 per cent of the hemicellulose was lost. The summary of the total losses of indigestible residue show that in six of the 10 materials fed from 53 to 74 per cent disappeared as they passed through the intestinal tract.

The three materials resistant to bacteria (bran, cotton seed hull, and alfalfa leaf) contained considerable amounts of lignin. That foodstuffs high in lignin are resistant to bacterial degradation in the intestinal tracts of

farm animals is well known. In Germany during the war the delignification of straw was studied; and it was found that the treatment of straw with alkali, which broke up the association of lignin and cellulose, resulted in a material much more nourishing to herbivorous animals (see Pringsheim). In our experiments lignin was not broken down when present in considerable quantity and, furthermore, its presence prevented the breakdown of both cellulose and hemicellulose. It has been previously pointed out that no increase in volume of stools occurred after the feeding of the two materials highest in lignin, i.e., cotton seed hull and alfalfa leaf.

Cellu flour is a material produced (according to the manufacturer) by "hydrolizing bleached fiber." In other words, it has been prepared in much the same way as crude fiber by the action of acid and alkali. We believe that this strong chemical treatment removes the portion of cellulose and hemicellulose which bacteria are able to attack and thus leaves it inert.

Mechanism of Laxative Action of Indigestible Residues

Since hemicellulose to a great extent and cellulose to a lesser degree disappear in passing through the human intestinal tract, they must be attacked by bacteria and if this be so, the metabolic products should be demonstrable. The products of carbohydrate residue breakdown are methane, carbon dioxide, hydrogen, alcohols and volatile fatty acids. Volatile fatty acids are easily determinable end products and are good indices of residue breakdown provided the soluble carbohydrate portion of the diet is regulated. Since these acids arise from the degradation of hemicellulose and cellulose, there should be a parallelism between the percentage of disappearance of those latter substances and the volume of volatile fatty acids recovered from the feces. Moreover since volatile fatty acids arising from any source (i.e. soluble or insoluble carbohydrates) are laxative, there should be a parallelism between the percentage disappearance of cellulose and hemicellulose, the stool content of volatile acids and the increment of stool weight. Table 7 shows this to be the case. The values are averages of three human subjects. The output of volatile acids formed after feeding those residues which were laxative exceeded those formed on high sugar diets.

In table 7 attention is called to the results in the case of agar agar. It was the most effectual of all materials fed in increasing the volumes of the stools. This substance is 81 per cent hemicellulose and therefore in comparison with the other types of indigestible materials fed, there should have been a greater percentage of the agar broken down and greater production of volatile fatty acids. That this was not so suggests that the effectiveness of agar is due to some other property which the other materials studied did not possess or possessed to a much less degree. The striking characteristic of agar is its ability to take up and hold water. It is this property which makes it such a fine foundation for culture media. The action of mineral cathartics is due to their ability to prevent the absorption of water by the

colonic epithelium. Any food residue that is highly hygroscopic keeps the feces pliable and plastic and makes for their easy evacuation by peristaltic rushes. If this explanation is correct, the hygroscopic property of the portion of food residues escaping bacterial degradation is of some importance and assists fecal evacuation. The effectiveness of agar is by no means wholly due to its hygroscopic property. Sixty per cent of the agar was broken down and the volume of fatty acids produced corresponded well with the amount of agar disappearing.

In brief, an effective residue is one which is free from lignin, contains a preponderance of hemicellulose, is finely divided so that bacteria may break it down into laxative products and which after bacterial action yields a remainder with water binding properties ensuring a bulky, plastic, easily evacuated stool.

TABLE VII

Relation of Increment in Stool Weight to Disappearance of Residue and Recovery of Volatile Fatty Acids

Materials Added to Basal Diet	Increment in Stool Wt.	Cellulose plus Hemicell. Disappearing	Increment Volatile Fatty Acids (0.1 N. Alk.)	Ratio: Increment Stool Wt. to Wt. Residue in Stool	Subjective Estimation of Laxative Value (1 Least)
	gm.	gm.	c.c.		
Cellu flour	93	7.4	35	1.45	2
Cotton seed hull	97	15.4	282	1.13	3
Canned peas	167	37.5	448	4.77	4
Alfalfa leaf	240	6.1	278	3.00	1
Sugar beet pulp	401	60.6	980	12.30	7
Wheat bran	475	41.2	1013	4.65	5
Carrots	541	74.4	970	19.30	9
Corn germ meal	578	89.0	1002	9.34	8
Cabbage	625	62.9	1352	17.90	10
Agar agar	666	48.6	896	20.80	6

SUMMARY

These researches into the physiology of bulky foods as represented by the 10 substances studied have led us to the following conclusions:

Of the three classes of substances which make up the effective portion of indigestible residues, the hemicelluloses are the most efficacious in increasing the bulk of the stool. Cellulose in its natural state is not as effective as the hemicelluloses. (We suspect that highly hygroscopic residues may be very effective.) Residues high in lignin are costive.

Contrary to the accepted belief, the effectiveness of indigestible residues is not due primarily to the mechanical stimulus of distention but rather to chemical stimuli which arise from the destruction of hemicelluloses and cellulose by the intestinal bacterial flora. One of these stimulating products is the lower volatile fatty acids. There may be others.

The chemical stimuli are aided by the hygroscopic quality of the residue escaping degradation. There may be other types of food residues in addition to the one studied here (agar) which are highly hygroscopic.

Finally, we are well aware of other properties of foods that render them laxative. The effectiveness of the soluble juices of apples and pears and other raw fruits has never to our knowledge been accurately studied. Nor has the well known laxative quality of dried prunes and figs been identified. Certainly we have presented evidence for the stimulating effects of sugars and starches when they predominate in the diet.

The physician should be aware of all these facts and make use of them when he feels it is for the benefit of his patient that the volume of the stool should be increased.

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OBSERVATIONS ON THE USE OF ACETYL BETA METHYLCHOLINE CHLORIDE IN CHRONIC ARTHRITIS *

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Many investigators have studied the value of choline compounds in the treatment of conditions involving vascular spasm. Acetylcholine has long been known but, because of its nicotine-like action, is not suitable for therapeutic use. Major and Kline [1] synthesized acetyl beta methylcholine chloride, a more stable compound, free from the nicotine-like side effects of previous compounds. When Starr [2] compared the action of acetyl beta methylcholine with acetylcholine, he found they had similar effects on the cardio-vascular system of animals when given intravenously. He also found acetyl beta methylcholine chloride more than 10 times as active as acetylcholine when given hypodermically in normal man; and in addition it could be given orally. Moreover, it lacked many of the undesirable side effects of acetylcholine. Starr believes acetyl beta methylcholine to be a superior choline compound and that it should replace acetylcholine for therapeutic purposes.

The pharmacologic reactions due to acetyl beta methylcholine are prompt and vigorous, and are similar to those which follow stimulation of the parasympathetic nerves. There is well marked peripheral vasodilation. This latter action has been investigated as to its value in conditions accompanied by, or due to vascular spasm. We undertook this present problem to ascertain the effect of acetyl beta methylcholine on the peripheral circulation. A group of 25 patients from the arthritis clinic of Northwestern University Medical School was selected. Although we are not convinced that there is a causal relation between the circulatory changes in arthritis, and the joint lesions, we do know that circulatory disturbances accompany and aggravate the disease. This has been shown by Pemberton [3] and others.

We realize the pitfalls attendant on the therapeutic study of this drug. This is particularly true in a field where measurement of success must depend on vague subjective changes and factors which are difficult to measure with accuracy. We have attempted to obtain objective measurements of observed changes after use of the drug; and to control these measurements under as nearly uniform conditions as possible, by identical observations on the same or similar patients on whom various types of therapy were used.

Acetyl beta methylcholine has been given to patients orally, subcutaneously and more recently by common ion transfer. When given by mouth the drug has a much milder effect and requires much larger dosage

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than is suitable for subcutaneous administration. Goldsmith [4] gave 50 to 150 milligrams by mouth without profound or uniformly appreciable effect on the blood pressure or pulse rate. Its action, when taken by mouth even in large dosage, was strikingly less effective than that produced by a 20 milligram dose given subcutaneously in the same patient.

Acetyl beta methylcholine is prompt and vigorous in action when given subcutaneously. Starr [2] states, "Its physiological activity is very great, being of an order similar to that of adrenalin or histamine." The striking systemic effects of the drug are a fall in blood pressure, a rise in pulse rate, flushing of the face and neck, sweating and salivation. This appears quickly, in one or two minutes after injection, and terminates in 15 or 20 minutes. It produces a constricting effect on the bronchioles, and transient asthmatic attacks have been produced by this drug in those susceptible. Its use also seems contraindicated in hypotension and in serious cardiac disease (except for its usefulness in attacks of paroxysmal tachycardia). In our series, we treated two cardiac patients, one of whom developed syncope and required atropine for relief, and the other suffered an aggravation of anginal pain. The former patient had a chronic rheumatic carditis, the latter had a coronary lesion. The drug should not be given intravenously because heart block may occur, particularly if the dosage is large (Katz [5]). Realizing this danger, we have not given acetyl beta methylcholine intravenously. We have seen no evidence of heart block in this series, giving the drug by common ion transfer. If untoward reactions do develop atropine abolishes the action of the drug almost immediately. We have found it necessary to use atropine only once,—in the cardiac patient mentioned above.

We gave acetyl beta methylcholine to our group of patients by the common ion transfer method, which in effect gives a slower, more gradual absorption from the superficial tissues. The constitutional effect of the drug appeared and in addition there was obtained a striking local reaction consisting of increased skin temperature, sweating, gooseflesh, faster capillary flow [6] and a diffuse pinkness of the skin over the area covered by the positive electrode. This reaction, we feel, is quite different from and more lasting than that of local counter-irritation. We feel that our controls (chart 1) demonstrate that it is definitely a local drug effect. This local effect at times lasted for 12 to 24 hours. We consistently found a decreased skin temperature distal to the treated area, whereas proximal to the treated area we always observed a rise in skin temperature of 2 to 4° F. This makes it necessary, when local effect on the hand is desired, to apply the positive electrode on the hand itself and not on the forearm proximal to it (figures 1, 2, 3). These marked local effects furnish the rationale for the use of acetyl beta methylcholine in this manner in arthritics.

We found that the drug consistently produced characteristic general reactions, which included a fall in blood pressure, averaging 12 millimeters of mercury and a rise in pulse rate averaging 22 beats per minute. Respiratory rate was unchanged, but most patients described a sense of heaviness in

CHART I

Table of Average Measurements and Reactions

Methods	Skin Temperature ° F.				Blood Pressure	P	R	Rectal Tem.	Pulse Vol. Wave	Reaction	
	Treated	Distal	Proximal 2"	Proximal 5"						Local	General
Mecholyl	96	82	94.3	92.4	−12	22	Deeper	No	Increase 3 × +	Heat, redness sweating	Salivation, sweating, heat, perspiration.
Histamine	94.3	83	92.5	91.5						Redness, wheals	None.
Heat lamp									Increase −2 ×		
Diathermy									Unchanged	Increased heat	None.
Galvanism	96	93			0	0			Unchanged	Redness, heat	Sl. perspiration.
Mecholyl (Hypo)							Labored		Unchanged	None	Profound disturb., cold extremities, labored resp., sub-sternal press.
Polar reversal mecholyl		93			0	0	0	0	Unchanged	Sl. local heat	Sensation heaviness limb.

Right Knee

12–14–34

Time	Skin Temp. Rt. Thigh	Blood Pressure	Pulse	General Reaction
3:05	91.0	125/80	88	Temp. mouth
3:10	91.0			5 M.A. Prickling sensation + Electrode
3:15	92.0	128/78	100	25 M.A. Salivation lacrimation
3:20	92.8	122/80	112	30 M.A. Salivation ++ Flushed cheeks
3:25	93.1	124/78	112	40 M.A. Sweating
3:28				Tremor. Feels she is having a chill
3:30	93.2	126/75	112	Fine tremor leg muscles continuing
3:35	92.9	124/92	96	Current off
3:40	92.5			Skin + Electrode red feels hot but temp. 87 Rt. 87 Lt.
				2nd treatment area + Electrode Before 87° F.
				After 91.4° F.
				Rise 4.4° F.

FIG. 1. Characteristic general and local reaction after acetyl beta methylcholine by ionization.

Left Knee

12–7–34

Time	Temp. Skin Dorsum Lt. Foot	Blood Pressure	Pulse	General Reaction
2:30	92.2	132/80	80	Knee painful, swollen limited motion
2:33	92.3		80	
2:35	92.4	122/80	80	5 M.A. Current
2:40	92.5	120/80	84	40 M.A. Heat at + Pole
2:50	92.5	118/78	93	50 M.A. + Nasal secretion
2:55	92.5	100/63	90	50 M.A. Sl. flushing
3:00	92.2	105/65	88	Current gradually off
3:07	92.0			Very little general reaction

FIG. 2. Less striking general reactions to acetyl beta methylcholine by ionization.

Galvanic Current Without Mecholin

− Rt. Elbow + Pole

5–16–34

Time	Skin Temp. Rt. Forearm	Blood Pressure	Pulse	General Reaction
10:45	92.3	98/?	54	
11:00	93.5	98/?	54	Saline solution + Electrode
11:15	92.5	98/?	54	Current on
11:30	93.2	98/60	54	30 M.A. No reaction
11:45	93.5	98/60	58	40 M.A. No reaction
12:00	93.8	98/70	68	No reaction
				Perspiration only
				Temp. over treated area
				96.1 After current
				93.1 Before current

FIG. 3. Control reactions using galvanic current without acetyl beta methylcholine.

the chest and inspired deeper. A flushing of the face, neck and ears occurred in all who experienced general reactions. Perspiration was usually marked, particularly about the face and neck, even in those who claimed to have had no perspiration in several years. Increased salivation and occasionally

lacrimation lasted one to two hours. One patient had increased saliva after each treatment for 12 to 24 hours. Body temperature by rectum, taken by mercury thermometer and by thermocouple, showed no change.

The general changes described are similar to those which follow subcutaneous injection, with the striking difference, however, that the effects came more gradually, caused much less distress and lasted longer. For our purpose the added local effect was a distinct advantage.

The reactions noted are specific ones due to drug action and not to current or heat effect. We have used the same technic in the same patient without acetyl beta methylcholine and none of the characteristic effects ascribed to the drug were observed. Further attempts to control this were made by local use of diathermy, infra red, and by reversing the current with the drug under the negative electrode. In none of these did we produce any general reaction, and the local effect of these heating agents was obviously less in degree and of a more transient nature.

Technic. We used a vacuum tube rectified direct current which gave a fairly smooth galvanic current (figure 4). The active electrode consisted of an asbestos fabric (resistant to tears) saturated with a 1 per cent solution of acetyl beta methylcholine chloride. Lower concentrations of the drug were tried, but we did not obtain satisfactory reactions with less than a 1 per cent solution. Kotkis and his associates,[6] working with dogs, reported no difference in drug effect with 1–1000, to 1–8000 solutions. They did, however, cover a relatively larger percentage of the skin area but did not mention the effect of stronger (1–100) solutions. We found a decided difference between the reactions obtained with a 1–100, and with a 1–200 solution. The weaker solution gave none of the clear-cut reactions illustrated in figures 1 and 2. The saturated fabric was wrapped in close contact about the part to be treated, and then a metal foil strip, three-eighths of an inch in width, was wound spirally about the saturated paper (figure 4). This metal strip was used to conduct the galvanic current evenly over the whole area. The positive pole of the galvanic current source was connected to the distal end of the metal strip. The negative pole of the machine was connected to the patient's back by means of a large dispersive electrode, 10″ by 12″ in size. This completed the circuit. The strength of current and the time of the current flow regulates the effectiveness of the ionization. We fully realize the limitations of introducing ions into living tissues by this method. Individual tolerance to the treatment guided us somewhat in the current strength, but we were usually able to give 40 to 50 milliamperes for 20 minutes after the first treatment. When the treatment was started, the current strength was gradually raised until the desired milliamperage was reached. Sudden increases should be avoided. At the end of treatment, the current intensity was gradually reduced until no current flowed. Following treatment the patient should remain quiet and warm for 30 to

60 minutes and then be allowed to resume his usual activities. When many joints are involved we have found it better to concentrate treatment on one joint or limited area,—such as the hand. The most satisfactory

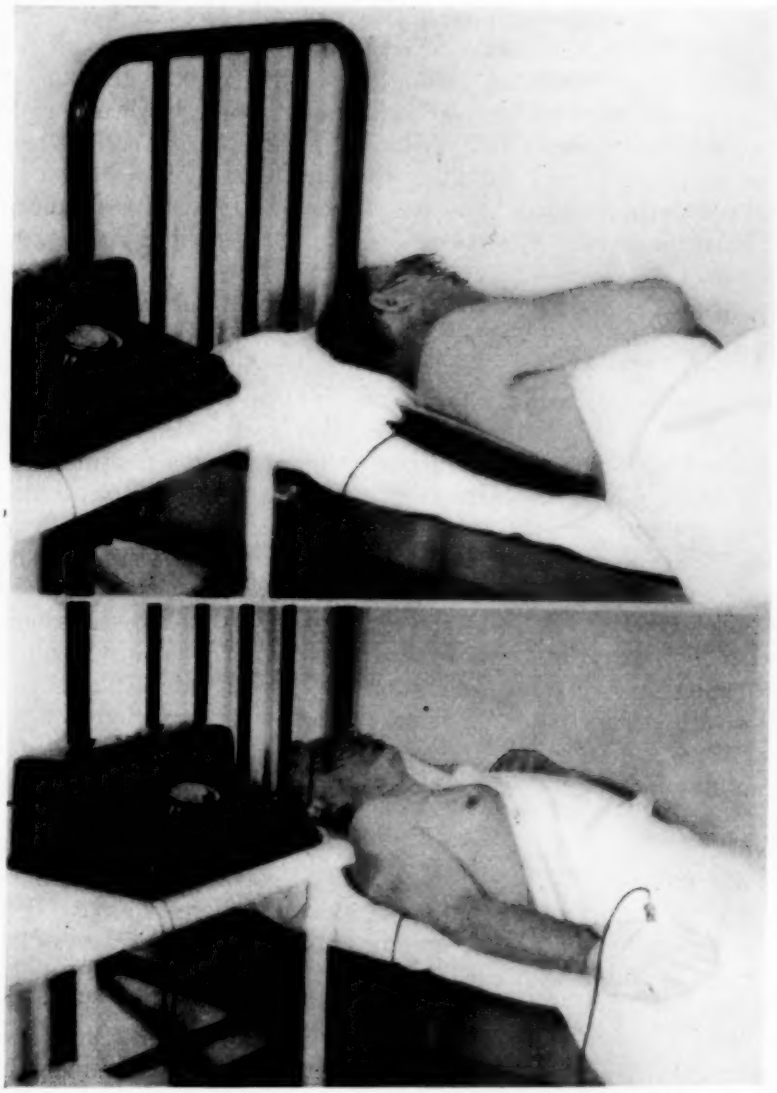

FIG. 4. Method of applying negative (above) and positive (below) electrodes for ionization of acetyl beta methylcholine.

interval between treatments appeared to be three or four days. The therapeutic effects on patients were studied after five, 10, 15, and 20 to 25 treatments. As a result of this check, we found the maximum effect was achieved after 18 to 20 treatments.

Acetyl beta methylcholine can produce undesirable reactions. Dosage when given subcutaneously must be accurate. One physician gave a subcutaneous dose of 250 milligrams of acetyl beta methylcholine which was 10 times that recommended as maximum. His patient had a severe reaction, but survived. Regardless of how this drug is given a hypodermic of atropine gr. 1/100 should always be prepared and available for use. Heart block can easily be produced in dogs, but they usually recover without atropine. These unfavorable reactions are minimized when the drug is given by common ion transfer. We have not had any very serious reactions, nor have we heard of any fatalities from its use. It is a drug of quick, powerful reactions, however, and should be as much respected as epinephrine.

We have treated 27 patients in the manner described during the past two and one-half years (chart 3). Earlier we made no attempt to select patients, as to the stage or type of their arthritis. It was soon evident, however, that certain less advanced arthritics derived more benefit than the far advanced. One would expect this, and it proved to be true in both the rheumatoid and osteoarthritic patients. Those with evident circulatory disturbances of the extremities—those with cool, pale, moist, and often cyanotic hands and feet—seemed to gain most from the treatment. All of our patients had had considerable previous medical treatment along the usual lines without much evident improvement. Acetyl beta methylcholine is not useful in those arthritic patients with peripheral arteriosclerosis nor is it feasible to treat patients with well distributed skin changes. It seemed most helpful in those who: (1) show the earlier changes of the rheumatoid type, with cool, damp and cyanosed extremities, (2) have moderate hypertrophic changes with paresthesias and sensitivity to cold, and (3) have sciatica or other manifestations of spinal nerve root irritation as a result of spinal arthritis.

In an attempt to gain objective evidence of the changes taking place, we have measured the pulse volume waves in the limb under treatment. These pulse volume wave changes were recorded graphically by the Johnson plethysmograph (chart 1). The graphic records, taken on the fingers before and after treatment of the hands, show an increased wave deflection, which is apparently dependent on the ability of the blood vessels in the studied part to dilate with each heart beat. Many cases of arthritis thus studied showed a surprisingly flat wave, as is illustrated in chart 2. One patient with a well marked peripheral arteriosclerosis showed a very small pulse volume wave both before and after acetyl beta methylcholine. Usually, however, the dilation of the vessels, as measured by the pulse volume wave, was increased after application of the drug (figure 5). We tried to keep conditions of the room and patients uniform in taking records. Although we did not have a constant temperature air-conditioned room, room temperature was taken into consideration. We consider this pulse volume wave record a better index of improved circulation in an arthritic member than observations of capillary changes in the nail fold. We do not believe that

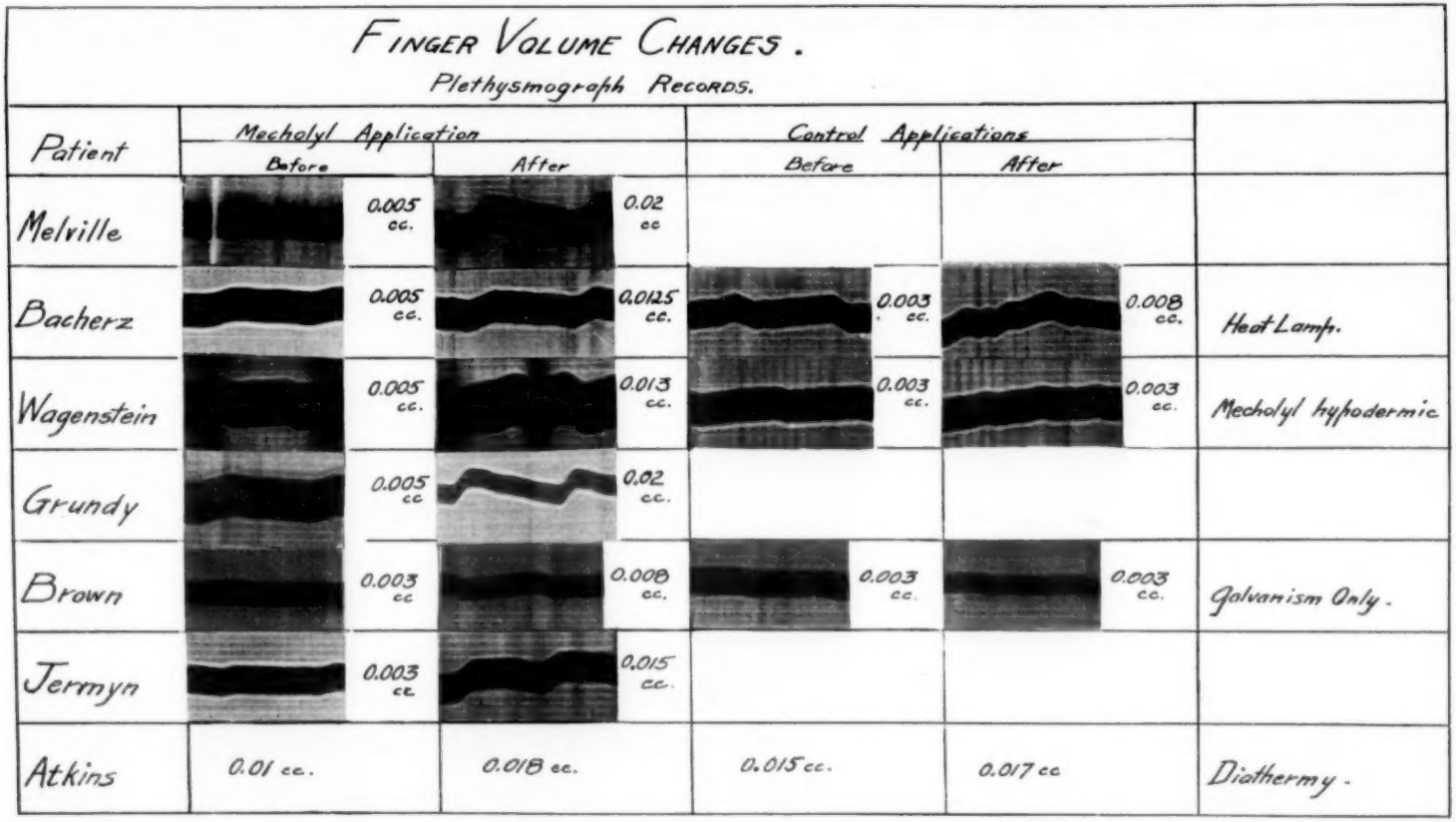

CHART II. Comparative finger volume changes with various types of treatment.

CHART III
Summary of Patients Treated, and Results

Patient	Age	Diagnosis	Duration of Disease	Complaint	Number of Treatments	Pain	Result Motion	Fatigue	Reactions		Complications	Duration Relief	Remarks
									Local	General			
A. M.	56	Hypertrophic arthritis	7 years	Pain, stiffness, paresthesia, fatigue	15 hands	Decrease	Increase	Disappeared	++++	++	Menopause	8 months	
T. U.	50	Hyper. arthritis; sciatica	3 years	Pain right hip, sciatic fatigue	21 sacral area	Relieved		Disappeared	++++	++	Myocarditis; secondary anemia	1 year	No interval treatment. No other treatment since. Strong and well.
K. T.	30	Infectious arthritis	2½ years	Pain, stiffness, fatigue	19 hands and knees	Decrease	Increase	Decreased	+++	++	Secondary anemia; chronic tonsillitis	1 year	
K. J.	24	Infectious arthritis	9 years	Total disability	19 hands	No effect			++	++		None	Disease too far advanced. Bone changes. Candidate for reconstructive surgery.
H. G.	35	Infectious arthritis	5 years	Pain, stiffness, left elbow	21 elbow	No effect			+++	++	Secondary anemia	None	May be gonorrheal arthritis
K. D.	23	Infectious arthritis	2 mos.	Pain, swelling, paresthesia wrists	17 hands	Relieved	Increased	Decreased	++	++	Obstinate constipation	10 months	
L. C.	12	Infectious arthritis	3 years	Pain, stiffness, polyarticular	27 hands and knees	No change			+++	+++	None	None	
A. K.	40	Infectious arthritis	2½ years	Pain, stiffness, polyarticular	7 hands	Slight improvement	Stopped treatment		+++	++	None		Stopped treatment.
E. G.	53	Mixed arthritis	5 years	Swelling, pain, knees	12 knee	No improvement			0	0	None		No reaction to drug.
M. S.	35	Infectious arthritis	many years	Polyarticular pains, stiffness	6	None	Stopped treatment		++	++	None		Did not continue treatment.
I. S.	39	Infectious arthritis	10 years	Polyarticular pains, deformities	20 hands	No change	Increased	Marked decrease	+++	+++	None	6 months	Gained weight, strength, use hands.
E. S.	51	Infectious arthritis	14 years	Pain, swelling, fingers, knees, shoulders	14 knees	Little change			++	+	Menopause; chronic infected tonsils	None	Stopped treatment.

CHART III—*Continued*

Patient	Age	Diagnosis	Duration of Disease	Complaint	Number of Treatments	Pain	Result Motion	Fatigue	Reactions		Complications	Duration Relief	Remarks
									Local	General			
B. R.	64	Infectious arthritis advanced	20 years	Polyarticular pains, deformities	16 hands	Unchanged	Increased	Unchanged	+	+	None	None	Never able to take adequate current for full drug effect.
L. H.	53	Hypertrophic arthritis	3¼ years	Pain, stiffness, weakness hands	15 hands	Decreased	Increased	Decreased	++	++	None	3 months	Marked increase in flexibility and use of the hands, fingers.
L. G.	68	Hypertrophic	16 years	Pain, stiffness, knees and hands	16 knees	No change	Increased	Decreased	+++	++	Senility	10 months	Stronger, more alert.
O. B.	48	Hypertrophic	Many	Paresthesias of fingers	20 hands	Decreased	Increased	Decreased	++	++	Gastric ulcer	1 month	
D. B.	30	Infectious	5 years	Low back pain; cold extremities	11 knees	Disappeared	No change	Decreased	++++	++	Obesity		Severe reaction. Required atropine.
S. W.	48	Hypertrophic	20 years	Pain, hands and knees	16 hands	No change	No change	No change	+++	+	Psychoneurosis		
F. R.	61	Hypertrophic	3 years	Pain, paresthesia of lower extremities	17 knee	Decreased	Increased	Disappeared	++	++	Chronic prostatitis	Still under treatment	Paresthesia and fatigue markedly relieved.
L. W.	31	Infectious	4 years	Fatigue, pain knees and back	13 knee	Disappeared	Increased	Disappeared	+++	++	None	Still under treatment	Four years medical treatment and no relief. Secured marked relief.
G. R.	39	Hypertrophic	3 years	Low back pain also referred to sciatic n.	19 low back	Decreased	No change	No change	++	++	Constipation; prostatitis	Still under treatment	Sciatic pain entirely relieved with few treatments
O. B.	40	Hypertrophic	3 years	Pain, stiffness to hands and knees	8 hands	No change	No change	No change	+	++	Psychoneurosis		
A. D.	34	Infectious	?	Pain, knees	8 knees	No change	No change	No change	++	++	Dementia praecox		
K. B.	44	Infectious	6 years	Pain, swelling hands and elbows	23 hands and knees	Decreased	Increased	Disappeared	++++	+++	None	10 months	
H. B.	56	Infectious	?	Pain and deformity of hands	2 hands	No change	No change	No change	++++	++	Coronary sclerosis		Unable to continue treatment due to cardiac condition.

a convincing characteristic capillary bed picture has been presented in arthritis.

Many patients showed not only a marked pulse volume wave increase in the member treated locally by common ion transfer but also minor increases in pulse volume wave in the opposite untreated member. Arthritics with cool, clammy hands showed in the first instance an almost flat curve, and

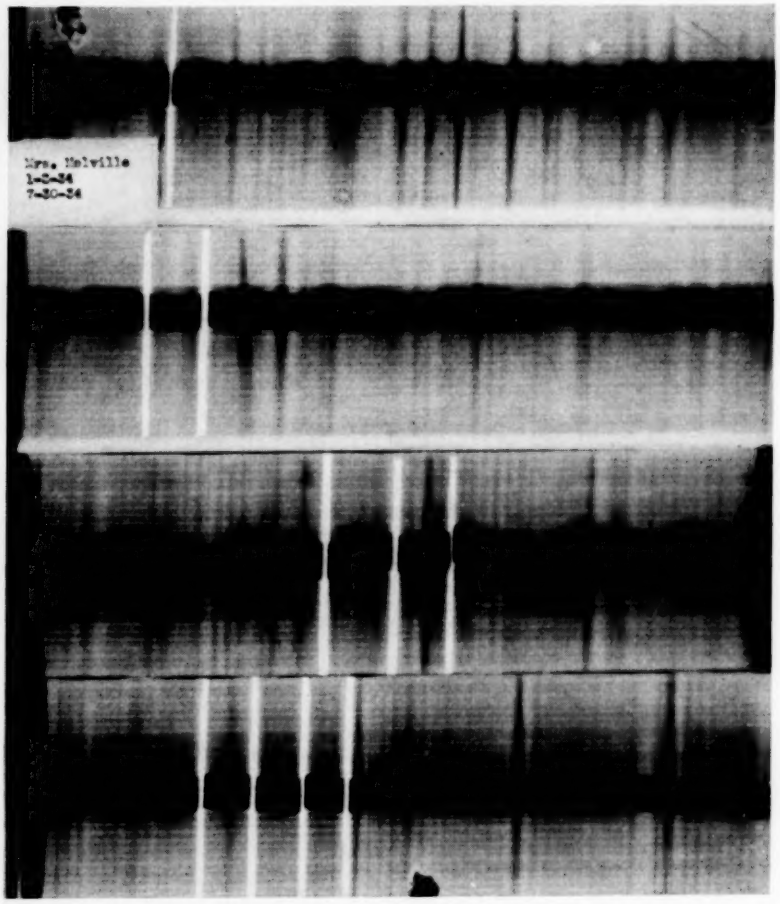

FIG. 5. Pulse volume wave of index finger (A.M.) before (1) and after (111) acetyl beta methylcholine applied to the hand.

after acetyl beta methylcholine a striking increase in the waves (figure 5). Given subcutaneously, the drug did not cause local changes in circulatory volume.

In the patients on whom control observations were made, the pulse volume waves were of a lower amplitude.

The well known cycles of improvement of arthritics and the lack of any well-defined measurable factors, make evaluation of therapy hazardous.

The recording of decreased pain and increased motion in function rests too largely on the patient's interpretation of his subjective sensations. With patients under continuous observation one can judge fairly well the extent of clinical improvement, but this rather intangible judgment is difficult to present to others. Nevertheless, we can offer no better measure for evaluating the present group.

The hands treated showed in 8 of the 14 patients an increased flexibility in function and usefulness in work. A patient, for example, who previously had been able to lift her coffee cup to her mouth only by using both hands, was able to do this with one hand in a normal manner. Another, forced to give up her work as a clerk and unable to do sewing, became able to work and sew again four days a week without discomfort for continuous periods of an hour or more. A young woman with considerable pain, stiffness and weakness in her hands who had been unable to do her housework for two years, reported a decided decrease in joint pain, improved motion, and a marked increase in strength. She became able to do all her housework except scrubbing floors and ironing. An older woman with lumbar and sacro-iliac arthritis, who complained of aching pains and constant fatigue to such an extent that she was comfortable only in bed, was treated over the area of her discomfort with the usual general reaction. After treatment, the low backache largely disappeared, " she felt quite strong again and was not so tired." Four months later without further treatment, she was much stronger, and without undue fatigability. A medical student observed an increased flexibility of the hands, a loss of considerable morning fatigue and joint stiffness, became much less tired and resumed walking and other outside activities. He noted the effect of the drug for three or four days following each treatment.

The group of failures in treatment were in general the elderly, far advanced rheumatoid arthritics with bone changes and fibrosis. In such advanced degrees of the disease much relief cannot be expected.

Striking relief of pain was afforded some cases, but as a record of therapeutic achievement in this respect, our results are only fair (chart 2). The striking therapeutic effect in the group is the decreased fatigability, and the increased endurance. This was consistently noted in almost all patients who absorbed the drug and took a sufficient number of treatments. Several patients resumed their normal activities, spent less time in bed, and carried on more work and play without increase of pain, stiffness or fatigue. This improvement in the endurance of our patients was called to our attention voluntarily and spontaneously, it being an unanticipated effect. We have not noted such a relief from fatigue under other forms of treatment. That this is a vital factor in the lives of most arthritics is constantly borne out by the complaints of most patients. Most workers in this field agree that rest sufficient to relieve fatigue is a most important element in the treatment of arthritic patients.[10]

Acetyl beta methylcholine does relieve fatigue in a large percentage of arthritic patients who are able to take adequate dosage. Whether this is due to its vasodilator effect, or some more direct effect on muscle, we do not know.

It is interesting that Hench [11] and his associates at the Mayo Clinic have treated this fatigue factor with amino-acetic acid and ephedrine. They report striking effects in certain patients, no effect at all in other apparently similar cases. No satisfactory measure of such fatigue has been proposed, though indirectly metabolic studies may help. It has not yet occurred to us how this factor may be measured. We believe that if fatigue can often be controlled, in many instances pain can be relieved, physical activity increased, and the morale of these patients raised considerably. It is this effect of mecholyl that impressed us most, and the prevalence of so many tired, physically restricted arthritic patients makes the continued use and study of the drug worth while.

Conclusions

1. Twenty-two cases of arthritis have been treated with acetyl beta methylcholine common ion transfer.
2. Eight of 14 patients whose hands were treated showed an increased flexibility in function and usefulness in these hands.
3. Pain was relieved in some cases.
4. Muscular fatigue was markedly relieved in almost all cases adequately treated.
5. Increased endurance was experienced by those completing the course of treatments.
6. Circulatory changes were graphically shown.
7. The group of failures were in general the elderly patients with far advanced rheumatoid arthritis with bone changes and fibrosis.
8. Patients with circulatory disturbances of the extremities; those with cool, pale, moist, and often cyanotic hands and feet gained most from treatment.
9. Maximum effects were gained after a series of 18 to 20 treatments.

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STUDIES IN HODGKIN'S DISEASE

III. CLINICAL APPLICATION OF THE GORDON TEST (A SYNDROME OF ATAXIA, SPASM AND PARALYSIS INDUCED IN RABBITS BY THE INTRACEREBRAL INJECTION OF EMULSIFIED HODGKIN'S TISSUE) *

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THE description by Gordon [1, 2] in 1932 of a biological test for Hodgkin's disease aroused widespread interest. Van Rooyen [3] in Scotland made a trial of the test and later, in a paper published in this country, van Rooyen and Olgivie [4] expressed the opinion that it had proved itself to be of definite clinical value. Our own evaluation of this test as a diagnostic aid in the differentiation of the Hodgkin's type of lymphoblastoma is presented here after three years of experience in which material from 16 cases of Hodgkin's disease and 30 cases of other types of lymphadenopathy has been tested.

Gordon's test consists of the injection of a saline or broth emulsion of lymph node tissue into the cerebrum of the rabbit. A positive test appears three or four days after such an injection when the animal loses weight, develops ataxia, stiffness of the legs and neck, spasticity and has convulsions on stimulation. If the animal survives, these signs of cerebral disease may disappear in two to four weeks leaving it quite normal; again animals may survive for weeks in the chronic active state and gradually develop paralysis of the hind quarters or even a quadriplegia. The above syndrome is not peculiar to the rabbit alone, nor is the reaction specific for Hodgkin's tissue. Kelser and King [11] have obtained a similar response in the guinea pig using both bone marrow and Hodgkin's tissue, and Friedemann [5] has pointed out that the proteolytic ferment of Jochmann [9] and his own acetone-alcohol-ether extract of normal human spleen, bone marrow or leukocytes may provoke a similar reaction.

METHODS

The specimens were obtained personally at operation, placed in a sterile Petri dish and taken to the laboratory. Here the extracapsular tissue was cleaned away under aseptic precautions and a transverse section, usually including one-third of the node, was removed for routine pathologic section. Another third of the node was cut with scissors into small bits and the tissue ground in a mortar with sterile normal saline or meat broth of pH 7.4. This heavy emulsion (approximately 15 per cent) was then cultured on aerobic and anaerobic media and part of the supernatant fluid

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immediately injected into the brains of rabbits. Cultures of the emulsions usually showed no growth but in a few, colonies of staphylococci or common contaminants appeared. Pure broth cultures of these organisms when injected into rabbit's brains did not produce a positive test. The remaining third of the lymph node and the unused portion of the emulsion were then stored at 5 to 10 degrees Centigrade.

Injection of the rabbit was done under ether anesthesia. With a small two-edged hand tool the skull was trephined at the angle formed by the junction of the occipital and central longitudinal ridge. This exposed relatively silent areas of the occipital lobe into which 0.35 to 0.45 c.c. of the emulsion was slowly injected. The skin wound was closed with Michel's clips and the animal returned to the cage. Following this the animals were weighed daily and watched for signs of a positive test.

Extracts of biopsied nodes and of bone marrow, liver and spleen obtained at autopsy were also made, using the method described by Friedemann.[5] The tissue was extracted in a mortar with acetone and at the end of 15 minutes the undissolved material was collected on filter paper and washed first with absolute alcohol and then with ether. The residue was allowed to dry and then mixed with an equal volume of 33 per cent glycerin in saline. After standing 24 hours the undissolved material was spun down and the supernatant glycerin mixed with five times its volume of a 2:1 alcohol-ether mixture. The resulting precipitate was allowed to settle out and then taken up in saline for injection.

Results

Table 1 shows the control series including lymphosarcoma, reticulum cell sarcoma, lymphoblastoma type undetermined, giant follicular lymphoma, hyperplasia, chronic inflammation, metastatic epidermoid carcinoma, mixed

Table I

Tissues Used as Controls for Gordon's Test

Diagnosis	Number of Cases	Rabbits Injected	Gordon's Test
Lymphosarcoma	10	20	20 Negative
Reticulum cell sarcoma	5	10	10 "
Lymphoblastoma? type	1	2	2 "
Giant follicular lymphoma	1	2	2 "
Hyperplasia	4	10	9 "
			1 Positive
Chronic inflammation	4	8	8 Negative
Epidermoid carcinoma	3	6	6 "
Mixed tumor of parotid	1	2	2 "
Dermoid cyst	1	2	2 "
Fetal tissue	1	2	2 "
Pseudo tumor of orbit	1	1	1 "
	32	65	64 Negative
			1 Positive

tumor of the parotid, dermoid cyst, fetal tissue and pseudo-tumor of the orbit. In all, 65 rabbits were injected with material from 32 patients. In only one case was a positive test obtained. This was from an emulsion of a lymph node from a seven year old girl who had an enlargement of the cervical and inguinal nodes for three years. The clinical impression was that she had Hodgkin's disease and, therefore she had received roentgen-ray treatment two years before entry. The nodes then decreased in size but had enlarged again during the year previous to coming into our clinic. A biopsy was done in the hope of establishing a diagnosis of lymphoblastoma but the pathological report was hyperplasia. Of three rabbits injected two remained normal while the third developed a weakly positive test. The diagnosis in this case is still uncertain, but 10 months after biopsy she was clinically in the end stages typical of Hodgkin's disease. Except for this case and one case of reticulum cell sarcoma the patients in the control series had received no roentgen-ray therapy before biopsy of the lymph node.

Gordon [2] remarked that this encephalitogenic agent was diminished or absent in fibrosed Hodgkin's glands but van Rooyen,[3] with whom we agree, could find no significant differences in the histologic structure of nodes giving a strong, weak or negative test.

Table 2 summarizes the results of tests with material from 16 untreated patients whose biopsied lymph nodes showed the histologic appearance typi-

TABLE II

16 Hodgkin's Tissues Used in Gordon's Test

	Number of Cases	Rabbits Injected	Gordon's Test	
			Positive	Negative
Cases having at least one positive test	9	58	46	12
Cases having all negative tests	7	21	0	21

cal of Hodgkin's disease. These 16 patients entered the hospital for the diagnosis of enlarged lymph nodes, often in one or both sides of the neck. They were usually young people (average age 26 years) who had noted the appearance of the masses from one month to two years before entry (average duration 5 months). In nine (56 per cent) of these cases the tests gave results which were considered positive while in seven the results were negative. However, in five of the nine one or more of the injected rabbits showed no reaction. In the other four cases all animals were positive. Van Rooyen [4] reports 75 per cent of all Hodgkin's cases as giving a positive test while Hanson [7] and van der Hoeden and Hulst [8] each report 60 per cent. Goldstein [12] found the test positive in seven of nine cases of Hodgkin's disease.

It is of interest at this point to note that in none of the other types of lymphoblastoma was a positive test obtained, in contrast to the finding of positive tests in over half the cases of the Hodgkin's type. This lends support to the belief that Hodgkin's disease may be separated from the lymphoblastoma group as a distinct entity.

The Nature and Pathology of the Encephalitogenic Agent

The properties of the agent producing these reactions in the rabbit have been investigated by Gordon,[1] MacKenzie and van Rooyen [6] and Kelser and King [11] and our observations here are in accord with theirs. Transmission of the agent from rabbit to rabbit was not effected and repeated injections of inert material did not sensitize rabbits to later injections of Hodgkin's material that had proved to be negative in rabbits that had not been previously injected. Evidently no immunity to the agent was produced as animals rendered positive and allowed to recuperate again became positive on injection of a second active emulsion. Likewise the serum of previously positive animals when added in equal quantities to an active emulsion did not inhibit the encephalitogenic factor.

The agent is remarkably stable. After preservation for 24 and 26 months at 5 to 10 degrees Centigrade and being considerably desiccated, two Hodgkin's nodes were emulsified and produced definitely positive Gordon tests. After exposure to 70 degrees Centigrade for one hour the agent loses its activity. The active principle is extracellular as cell free supernatant fluids give positive tests. The agent in saline emulsions could not be passed through a filter (Berkefeld N) and application of the emulsion to the scarified cornea of rabbits provoked no signs of either encephalitis or keratitis. Recently van Rooyen [6] has found that the maximum effect of the agent is obtained if the broth is adjusted to a pH of 6.8 to 7.3 and that by so adjusting the Seitz and Berkefeld candles he could successfully pass the agent through the filter. It is well known that meat broth itself will change the retentiveness of a Berkefeld filter,[10] so that this may in part explain his results.

Friedemann [5] recalled that this reaction of the rabbit after the injection of Hodgkin's gland emulsion was not specific, as Jochmann and Lockemann [9] had found a proteolytic ferment in extracts of normal spleen, white blood cells and bone marrow of man and monkey that produced identical effects in rabbits. Friedemann's modified technic, the acetone-alcohol-ether extract described here under methods, has also yielded an encephalitogenic factor that produces positive Gordon tests. Friedemann assumed that a virus or bacteria could not withstand such processing, but MacKenzie and van Rooyen [6] have since found that it is not necessarily lethal to certain bacteria. In addition to the tissues mentioned above we found that such an extract of normal human liver would produce a positive test.

From two cases of Hodgkin's disease both the broth emulsions and the acetone-alcohol-ether extracts of diseased nodes gave typical positive Gordon tests while from a third case neither caused a reaction in the rabbits. From three control cases (reticulum cell sarcoma, lymphosarcoma and lymphoblastoma type undetermined) neither the emulsions nor the extracts caused any reaction in rabbits.

The exact nature of this agent is still unknown but as shown above it lacks many of the characteristics of a virus. Gordon mentioned the similarity of the reaction to the meningo-encephalitis produced by the virus of dermo-vaccine, herpes and psittacosis and the remarkable stability, like the virus of swine fever. In a recent publication MacKenzie and van Rooyen [6] found that the proteolytic ferment of Jochmann could be identified separately from the agent obtained by the methods of Gordon and Friedemann. As indicated in the six cases last mentioned the agent can withstand rather drastic extraction with acetone-alcohol-ether and what is more important, it is not present in lymph nodes giving a negative Gordon test.

Autopsies were done on rabbits killed with ether. Those found dead in their cages were not examined. The brains usually appeared normal in the gross except for some hyperemia about the site of injection, although in two gross signs of meningitis were found. Cultures of the injected areas yielded no growth and no evidence of the parasite *Encephalitozoon cuniculi* could be found. Microscopic examination showed changes, usually in one or both hemispheres. A perivascular infiltration of mononuclear cells resembling monocytes and lymphocytes was the predominant lesion but meningeal infiltration and occasional focal collections of these large mononuclear cells were observed. While these changes were observed in all the positive cases they were very slight in three animals and a slight meningeal reaction was present in several of the negative ones. Consequently it is felt that no definite conclusions can be drawn as to the significance of the findings. One can probably go so far as to say that the changes observed, because of the inconspicuous microglial reaction, do not resemble the picture commonly found with virus diseases of the brain. The histo-pathologic aspects of the problem invite a more thorough examination of positive animals and careful comparison with a larger number of injected negative and untreated animals.

Summary

From nine of 16 cases (56 per cent) of microscopically typical Hodgkin's disease positive Gordon tests were obtained, but of 58 rabbits injected with material from these nine there were 12 rabbits that showed no reaction. In a control group of tissues from 32 cases of other pathological conditions 31 gave negative tests. In the one control case described the patient may have had Hodgkin's disease and yet two of the three rabbits injected were negative. The encephalitogenic agent which produces this response in the rabbit is not specific for Hodgkin's tissue for it may be extracted from nor-

mal human marrow, spleen, liver and leukocytes. It was not obtained from eight lymph nodes showing hyperplasia or chronic inflammation. Knowledge of this agent is limited but it appears that it is not a virus and as it will withstand acetone-alcohol-ether extraction it may be a non-living substance simply acting as a profound irritant to nerve tissue.

Conclusions

Gordon's test, if positive, is only of supportive aid in the diagnosis of Hodgkin's disease and if negative does not exclude it. Therefore, this test should not replace the routine pathologic examination of tissue for diagnosis. The absence of the encephalitogenic agent in the first four types of lymphoblastoma (lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and lymphoblastoma type undetermined) adds support to the belief that Hodgkin's disease is a separate clinical and pathological entity.

The author is indebted to Miss Helen Roach for technical assistance and to Dr. Chas. S. Kubik for reviewing the pathology of the brain lesions.

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THE COURSE OF HYPERTENSIVE HEART DISEASE *

I. AGE OF ONSET, DEVELOPMENT OF CARDIAC INSUFFICIENCY, DURATION OF LIFE, AND CAUSE OF DEATH *

By NATHAN FLAXMAN, M.D., *Chicago, Illinois*

ARTERIAL hypertension is the most common cause of heart disease in adults regardless of race or sex.[1] There has developed in the last two decades especially an overwhelming literature devoted to this subject which, as Crummer [2] states, has almost buried from our modern view the earlier and fundamental observations. Janeway's [3] classical analysis of 870 cases of hypertensive cardiovascular disease (nephritis included) first indicated that the most prominent symptoms associated with hypertension are circulatory and that in the presence of early symptoms of myocardial weakness a better than 50 per cent chance existed that death eventually would be due to myocardial insufficiency. Fahr,[4] who added greatly in these earlier days to our knowledge of hypertensive heart disease, found that arterial hypertension by its direct or indirect effects on the heart muscle was the chief etiologic factor in approximately three-fourths of the cases of so-called chronic myocarditis.

The present study on the course of hypertensive heart disease was begun on December 31, 1931. In the following four years 1170 cases of hypertensive heart disease were examined and their histories carefully analyzed. Cases with complicating heart disease of other origin such as those with lesions due to syphilis, rheumatic fever, or thyrotoxicosis, or hypertension the result of glomerulonephritis, and cases with insufficient data were excluded. There remained for analysis 623 uncomplicated cases of hypertensive heart disease. The criteria followed for the diagnoses were those approved by the American Heart Association.[5]

The exact duration of the essential hypertension was not known in any of the cases. Only 31 patients (3.7 per cent) had known of the existence of their hypertension for from one to 12 years prior to the onset of symptoms. In this group the average known duration was five years.

The symptoms that indicated the onset of hypertensive heart disease were dyspnea, precordial or epigastric pain or both, palpitation, weakness, persistent indigestion, and marked loss in weight. Only 6.6 per cent of the white patients were below 40 years of age at the onset of symptoms, but 16.6 per cent of the colored patients were below that age (table 1). The largest incidence among the colored patients occurred in the decade from 41 to 50 years (47.6 per cent); while among the white patients the highest incidence fell in the sixth decade, 51 to 60 years (49.7 per cent).

* Received for publication July 20, 1936.
From the Cook County Hospital (1932–1933),[1] the Mercy Free Dispensary of Loyola University Medical School (1933–1934), and the Out-Patient Dispensary of the Mt. Sinai Hospital (Service of Dr. Harry J. Isaacs).

TABLE I

Percentage in the Age Groups

Ages	White				Colored			
	M.	F.	Total	%	M.	F.	Total	%
21–30	0	1	1	0.3	4	1	5	2.6
31–40	18	9	27	6.3	19	8	27	14.0
41–50	97	28	125	29.1	64	28	92	47.6
51–60	176	38	214	49.7	47	9	56	29.0
61–70	45	18	63	14.6	10	3	13	6.8
Totals	336	94	430	100.0	144	49	193	100.0
	69.0%				31.0%			

The duration of the disease was estimated in 189 known deceased patients from the onset of the first symptom. Later the data on 434 known living patients were studied in order to compare the duration in the deceased and in the living patients (table 2). Of the deceased white 80.8 per cent

TABLE II

Duration of Disease after Onset of Cardiac Symptoms

Duration	Deceased								Living							
	White				Colored				White				Colored			
	M.	F.	T.	%	M.	F.	T.	%	M.	F.	T.	%	M.	F.	T.	%
1 Day–6 Months	52	9	61	51.3	28	12	40	57.2	125	37	162	53.4	47	17	64	52.1
7 Months–1 Year	17	4	21	17.7	12	1	13	18.5	33	9	42	13.7	19	7	26	21.1
2–5 Years	25	7	32	26.9	13	2	15	21.5	69	15	84	27.6	22	5	27	22.1
6–10 Years	2	2	4	3.3	0	1	1	1.4	7	9	16	5.0	3	2	5	3.9
11–20 Years	1	0	1	0.8	0	1	1	1.4	1	0	1	0.3	0	1	1	0.8
Totals	97	22	119	100.0	53	17	70	100.0	235	70	305	100.0	91	32	123	100.0

and of the deceased colored patients 84.5 per cent had died within two years after the onset of symptoms. A comparison with the percentage of living patients who were observed within two years after the onset of symptoms indicated the same ratio, 77.6 per cent of the living white and 82.1 per cent of the living colored patients. The only similar figures available for comparison are those of Janeway [3] who reported that the average duration of life in his group of well-to-do patients after the onset of symptoms was four years in men and five years in women.

The symptoms were usually slowly progressive after an insidious onset but the numerous exceptions made attempts to estimate prognoses very difficult. The life-expectancy was short when the symptoms appeared suddenly and were not preceded by any omens of cardiac distress. The average duration of symptoms before the occurrence of heart failure was one year. The main reason for the short interval between the onset of symptoms and the appearance of congestive heart failure appeared to be the sufferers' reluctance to seek available medical attention for the relief of symptoms. Many of the patients continued to work and struggle along in spite of evident heart failure. Some delayed going to bed until the symptoms of failure became so pronounced that they no longer could stand on their feet. Such unnecessary delays led to the death of patients early in the course of the disease.

A comparison of the duration of the disease after the onset of congestive heart failure in the known deceased and in the living patients indicates approximately similar percentages (table 3). Of the deceased white 89.2 per

TABLE III

Duration of Disease after Onset of Congestive Heart Failure

Duration	Deceased								Living							
	White				Colored				White				Colored			
	M.	F.	T.	%	M.	F.	T.	%	M.	F.	T.	%	M.	F.	T.	%
1 Day–6 Months..	72	10	82	74.0	41	13	54	78.4	183	51	234	76.9	74	21	95	77.9
7 Months–1 Year...	13	4	17	15.2	6	1	7	10.1	26	9	35	11.4	5	7	12	9.8
2–5 Years..	6	5	11	9.9	6	1	7	10.1	25	10	35	11.4	11	2	13	10.7
6–10 Years.	0	1	1	0.9	0	0	0	0.0	0	1	1	0.3	0	2	2	1.6
11–20 Years...	0	0	0	0.0	0	1	1	1.4	0	0	0	0.0	0	0	0	0.0
Totals.....	91	20	111	100.0	53	16	69	100.0	234	71	305	100.0	90	32	122	100.0

cent and of the deceased colored patients 88.5 per cent had died within one year after the occurrence of congestive heart failure. The percentages of living patients who came under observation within one year after congestive failure occurred were, in the white 88.4 per cent and in the colored patients 88.0 per cent.

As to the age at death in hypertensive heart disease, table 4 indicates that 30.2 per cent of the white and 65.2 per cent of the colored patients had died before they were 50 years old.

The common cause of death was congestive heart failure, as table 5 indicates. Uremia was the next most common cause of death; it was more frequent in the colored patients and in the males of both races. Coronary thrombosis and cerebral hemorrhage were the causes of death of many

TABLE IV
Percentage of the Age Groups at Death

Ages	White				Colored			
	M.	F.	T.	%	M.	F.	T.	%
21–30	0	0	0	0.0	1	0	1	1.4
31–40	4	1	5	4.1	5	3	8	11.6
41–50	25	6	31	26.1	25	11	36	52.2
51–60	52	8	60	50.5	14	3	17	24.6
61–70	16	7	23	19.3	7	0	7	10.2
Totals	97	22	119	100.0	52	17	69	100.0

TABLE V
Percentage of Causes of Death in 189 Cases

Causes of Death	White				Colored			
	M.	F.	T.	%	M.	F.	T.	%
1. Congestive heart failure	63	14	77	64.8	32	13	45	64.3
2. Uremia	13	4	17	14.3	11	3	14	20.1
3. Coronary thrombosis	13	0	13	10.9	2	0	2	2.8
4. Cerebral hemorrhage	3	3	6	5.2	6	1	7	10.0
5. Ruptured dissecting aortic aneurysm	1	0	1	0.8	1	0	1	1.4
6. Spontaneous rupture ascending aorta	0	0	0	0	1	0	1	1.4
7. Adams-Stokes syndrome	1	0	1	0.8	0	0	0	0
8. Diabetic coma	1	0	1	0.8	0	0	0	0
9. Mesenteric thrombosis	1	0	1	0.8	0	0	0	0
10. Incarcerated inguinal hernia	1	0	1	0.8	0	0	0	0
11. Septicemia	0	1	1	0.8	0	0	0	0
Totals	97	22	119	100.0	53	17	70	100.0

patients, especially of those who died within one week after the sudden onset of symptoms. Coronary thrombosis was found to be the third most frequent cause of death. Its highest incidence was in white males (table 6).

TABLE VI
Additional Factors in the 623 Cases

Conditions	White				Colored			
	M.	F.	T.	% of Total (430)	M.	F.	T.	% of Total (193)
1. Coronary thrombosis	29	2	31	7.2	4	1	5	2.5
2. Angina pectoris	13	2	15	3.5	1	0	1	0.5
3. Positive blood Kahn tests	9	4	13	3.0	33	7	40	20.7
4. Cerebral hemorrhage	8	4	12	2.8	11	2	13	6.7
5. Diabetes mellitus	8	3	11	2.5*	1	2	3	1.5
6. Obesity	8	1	9	2.1	0	1	1	0.5
7. Sudden death	5	0	5	1.1	1	0	1	0.5
8. Pulmonary tuberculosis	2	1	3	0.7	0	0	0	0

Comment

Since an analysis of the course of hypertensive heart disease might not be fairly representative if it were based exclusively on data from the records of deceased patients, there has been included in this study comparative figures drawn from the records of living patients.

The short duration of life (two years or less in approximately 80 per cent of the deceased patients) may be accounted for in part by the fact that in the class of patients studied medical attention was not sought until the disease had made marked headway. Janeway, whose series included chiefly patients from the well-to-do, stated that one-half of the whole number of the deceased died within the first five years; one-fourth lived between five and 10 years; and the remaining one-fourth lived over 10 years. Because of the striking variations in the duration of the disease he advised great caution in prognosis. In this series of cases eight deceased patients had lived five to 10 years after the onset of symptoms and we found 26 patients who were living after five to 10 years. Two deceased patients had lived, and seven patients are living 10 to 20 years after the appearance of symptoms.

Two of the deceased patients had lived longer than five years after the onset of congestive heart failure, and at the conclusion of the study there were seven patients living five to eight years after the first appearance of congestive failure.

Summary

The course of hypertensive heart disease based on a four year study of 623 uncomplicated cases (189 known dead and 434 known living) is reported. Approximately 80 per cent of the deceased succumbed within two years after the onset of symptoms. Congestive heart failure occurred most frequently within one year after the onset of symptoms, and 85 per cent of the deceased had died within one year after heart failure appeared. The majority of the deceased colored patients (65.2 per cent) died before 50 years of age, while a minority of the deceased white patients (30.2 per cent) succumbed before that age. Sixty-five per cent of the deceased died of congestive heart failure, although all of the patients had evidence of heart failure at some time during the course of the disease or at the time of death.

A significant number of patients, although very small in comparison with the remainder, had lived or are still living five to 20 years after the appearance of the first symptom, and a lesser group had lived or are living five to eight years after the occurrence of congestive heart failure.

It is a pleasure to express my indebtedness to Dr. Italo F. Volini from whom much encouragement to carry out this study was derived.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1935 *

(Third Rheumatism Review)

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This Third Rheumatism Review was prepared at the request of the American Association for the Study and Control of Rheumatic Diseases. The editorial comments express the opinion, not of the Association but of its editorial committee (the authors of the Review) of which Dr. Hench is Chairman.

DURING 1935, medical literature published in English contained over 600 articles on diseases of joints and related tissues and on allied subjects, which have been surveyed for this Third Rheumatism Review. This number is a substantial increase over that of previous years, an increase due in part to the greater amount of investigative work being reported, but particularly to the number of short synopses and reviews presented by physicians to county and state societies. Making few or no pretensions to original researches, many of these papers contained little suitable for this review. But they have a significance not to be overlooked. For the most part they reflect a sound, broadened view of the problem of rheumatism, and provide definite evidence of the growing interest of the medical profession therein. The general practitioner is no longer willing to ignore rheumatism, content with the sorry gesture of salicylates for his new, and spas for his old, arthritic patients. His mind is in ferment, his interest is aroused. His is now a more resolute inquiry, increasingly purposeful and critical. The slogan of the few is becoming that of the many: Something must be done to solve the enormous problem that is "rheumatism."

GENERAL INCIDENCE AND OCCUPATIONAL DISTRIBUTION

Statistics given in previous Reviews [1, 2] show all too well how great a social and economic problem rheumatic diseases are creating. Rheumatic fever and "nonspecific arthritis" were found to be "world problems" in a recent survey on "The Geography of Disease" by the Division of Medical Sciences of the National Research Council.[3] Rheumatism apparently knows no boundaries of climate or geography, and few indeed are the countries not widely affected thereby.

Occupational factors play a definite rôle in the incidence of rheumatic diseases; but statistics on the relation of industrial environment to the incidence and course of these diseases have generally been inadequate, according to Buckley,[4] because neither the patient's occupation nor the exact type of his disease has been carefully classified. Buckley noted that coal miners and others who work underground at warm temperatures and high humidities are much (50 per cent) less subject to atrophic and hypertrophic arthritis than the general male population of Buxton, England, but are much (50 per cent) more prone to fibrositis. Stokers and others engaged in "hot occupations" seem much less susceptible to atrophic or hypertrophic arthritis, rheumatic fever, or fibrositis, but seem prone to gout. Of those reporting to the Devonshire Hospital because of "rheumatism," 8 per cent had gout. A possible cause was considered to be loss of perspiration, an altered saline content of tissue, and changes in the solubility of sodium biurate. Outdoor workers suffer oftener from atrophic arthritis and from rheumatic fever, indoor workers from hypertrophic arthritis and from fibrositis.

Classification of Diseases of Joints and Related Structures

A general familiarity with terms used by various writers is the first step toward a universal classification of rheumatic diseases. By this token the year's literature indicates some progress. Although writers have continued to use favorite designations, they have with increasing frequency appended the synonyms of others, indicating familiarity therewith. Some have adopted the classification used in our previous Reviews which embodies that approved by the American Committee for the Control of Rheumatism. The year's crop of "new classifications" is small. In general they are but minor modifications of old classifications, or are sometimes proposed without adequate clinical or pathologic foundation to invite our acceptance of them. None seems subject to less criticism than that used in our previous reviews. Hence they will not be copied here to add to the reader's confusion.

Diseases of joints and related structures may be briefly classified as follows: (1) those due to trauma; (2) those due to infections of known type; (3) those of unknown cause but possibly, or probably, due to infection or related toxins, for example, rheumatic fever, atrophic (infectious, proliferative, rheumatoid) arthritis; (4) those of unknown cause and of which the chief characteristic is degenerative change in tissue, for example, hypertrophic (senescent, degenerative, osteo-) arthritis; (5) those of which the chief or only obvious characteristic is some recognizable chemical derangement—a none too well defined group which includes gouty and hemophilic arthritis and the arthritis of serum sickness as well as certain forms of arthritis called "chemical," "metabolic," "allergic," "endocrine," and (6) a miscellaneous group of unclassifiable types. For a detailed amplification of this classification and our own criticism of it and of other classifications the reader is referred to the first review.[1]

It would be advantageous for physicians of at least the two great English-speaking nations to employ the same classification. To this end the provisional classification adopted by the Subcommittee on Nomenclature of the British Committee on Chronic Rheumatism is given herewith, and attention is called to their excellent first Report[5] which includes a full discussion of the pathologic criteria used for this classification:

Group 1. Rheumatic fever, acute (Syn.: "Acute Rheumatism") or subacute.
Group 2. Acute gout.
Group 3. Chronic arthritis.
A. Rheumatoid type ("atrophic; proliferative").
1. Specific causation. Known etiology.
(1) Gonococcal arthritis.
(2) Tuberculous arthritis.
(3) Syphilitic arthritis.
(4) Arthritis following other specific infections such as dysentery, scarlet fever, rheumatic fever.

2. Nonspecific causation. Unknown etiology.
   (1) With known associated factors.
      (*a*) Metastatic or "focal" arthritis, including so-called "multiple infective arthritis."
      (*b*) Associated with disordered metabolism (e.g., gout).
      (*c*) Climacteric arthritis (villous type).
   (2) With no known associated factors.
      (*a*) Classical type of rheumatoid arthritis of women, usually of child-bearing period.
      (*b*) Rheumatoid arthritis in children, including Still's disease.

   The term "rheumatoid arthritis," when utilized, should be confined to the above two conditions, all other forms being designated "rheumatoid type."

B. Osteo-arthritic type ("hypertrophic"; "degenerative").
1. Known etiology.
   (1) Secondary to trauma.
   (2) Secondary to arthritis of rheumatoid type.
   (3) Associated with disordered metabolism (climacteric, gout, scurvy, hemophilia).
   (4) Associated with organic disease of the nervous system (e.g., Charcot's joints and syringomyelia).
2. Unknown etiology.
   So-called "senile variety" (e.g., morbus coxae senilis).

Group 4. Non-articular rheumatic affections.

Diseases of Articular and Periarticular Tissues Related to Trauma

Acute trauma or prolonged or repeated trauma may initiate reactions in articular and periarticular tissues resulting in either an arthritis, synovitis, tendinitis, bursitis, or myositis. The type and extent of the reaction depends on the nature, location and severity of the injury, and resistance of affected tissues and their powers of regeneration. The reaction to trauma to synovial tissue, which has high regenerative powers, will not be the same as that to cartilage, which has feeble powers of regeneration. Trauma may produce arthritis in a previously healthy joint, or it may aggravate a preexisting arthritis. These two types of traumatic arthritis should be differentiated.

Articular Disease Due Primarily to Trauma. When an injury is promptly followed by an acute reaction of swelling, redness, stiffness, muscle spasm and within a relatively short time by roentgenographic changes, a diagnosis of traumatic arthritis is obvious. Diagnosis may be difficult when a delay elapses between injury and the onset of symptoms. Then the question arises whether such an arthritis, manifesting itself after a period of quiescence following an accident, is truly traumatic in origin. According to Bick [6] a direct blow to an elbow for instance rarely causes immediate damage to cartilage but may disrupt periarticular vessels and produce a vascular disturbance, the cause of later intra-articular changes. Certain criteria for

the diagnosis of traumatic arthritis should control "the well meant but prejudiced testimony of the claimant's physician, as well as the doubts of the impartial or defender's examiner." Bick's criteria follow: (1) one should know whether articular function was normal before injury; if the joint was previously affected one must know the degree of previous disability; (2) a diagnosis of traumatic arthritis is not justified in the presence of normal joint function—full painless motion; (3) the presence of pain alone is not enough to justify the diagnosis of intra-articular disease; periarticular disease may account for it, and (4) muscle spasm and definite limitations of motion are generally present. Variations from normal range of motion, the presence of any motion not characteristic of a joint, or variations of resistance at the extremes of motion are ipso facto evidence of disease.

Not all patients without roentgenographic alterations are malingerers. Intra-articular disease may be absent or insufficient in amount to produce them, but periarticular disease (such as rupture of a supraspinatus muscle) may be present. In the absence of roentgen-ray alterations diagnosis rests on clinical findings: swelling, tenderness, painful limited motion.

A "temporo-mandibular joint syndrome," described by Costen [7, 8, 9] may arise from mal-occlusion of natural or artificial teeth or in edentulous mouths. Mandibular joint destruction may result from lack of molar teeth or badly fitting dental plates permitting overbite: articular destruction may be unilateral from one-sided, poor molar support. Symptoms are variable and include constant or intermittent catarrhal deafness, "stuffiness" of ears, tinnitus, snapping noises in ears while chewing, dull pain in and about ears with or without herpes of the external canal and buccal mucosa, dizziness (generally mild, sometimes severe), severe constant headaches which may be vertical, occipital or postauricular and which persist after "sinusitis" is treated, glossodynia or burning pain in the throat or side of nose, and tenderness over mandibular joints. Symptoms may be promptly relieved by inflating eustachian tubes or interposing disks between the jaws. Roentgenograms may show erosion of heads of condyles and articular eminences. Symptoms are produced by erosion of the bone of the glenoid or mandibular fossa, impaction of condyles against the thin bone separating them from the dura and its rich nerve supply, irritation of the auriculotemporal nerve, reflex pain and sensory disturbances in the chorda tympani nerve. Treatment consists of repositioning the jaws by proper dentures which move condyles away from the range of the chorda tympani and auriculotemporal nerves.

(No description of the micropathology of joints was given.—Ed.)

Articular Disease Aggravated by Trauma. If an injured patient is found to have had previous symptoms in other joints, a mild atrophic arthritis may be present (Bick [6]). The assessment of disability is difficult for patients who after injury are found to have hypertrophic changes in the

spine, hips or knees. These changes may have long antedated the injury and may represent, not traumatic hypertrophic arthritis, but senescent hypertrophic arthritis which is so common in men over 40 years of age and which may be symptomless. Such a condition may be aggravated or made symptomatic by injury. The effect of injury can be evaluated only by noting the degree of greater functional and roentgenographic abnormality on the injured side than on the opposite side affected only by senescent hypertrophic arthritis.

Pathologic and Roentgenographic Alterations. According to Bick,[6] the primary reaction in traumatic arthritis is invariably synovitis, " a congestion of synovial and subsynovial strata." Allison and Ghormley (1931) showed that when cartilage is affected, a degenerative arthritis may be produced: fibrillation and degeneration of cartilage. Secondary reactions in articular bone may occur, producing roentgenographic changes hypertrophic in nature. Roentgenographic alterations in traumatic hypertrophic arthritis therefore may resemble those in senescent hypertrophic (osteo-) arthritis. That two such widely different causes (acute trauma on one hand, and presumably a chronic degenerative process of age and wear and tear on the other) may produce similar roentgenographic abnormalities indicated to McMurray[10] that " hypertrophic arthritis " (in the roentgenographic sense) is not one disease but a reaction of articular tissues to several different agents (including gout and gonorrhea.—Ed.). It must be borne in mind, then, that roentgenographic " hypertrophic arthritis " is not necessarily either traumatic hypertrophic arthritis or senescent hypertrophic (osteo-) arthritis. McMurray[10] and Doub[11] believed that monarticular hypertrophic arthritis, particularly of a hip, probably represents traumatic hypertrophic arthritis, but bilateral hypertrophic arthritis represents the syndrome of senescent hypertrophic (degenerative, osteo-) arthritis.

Doub and Jones[12] were unable to prove that single, severe trauma produced hypertrophic arthritis. Thirty patients, aged 12 to 71 years (average 44), suffered fracture of one of the long bones of a leg. Eight months after injury there was no evidence of arthritis of adjacent hips or knees in 28 cases. In one case moderate hypertrophic arthritis of a knee, present before injury, was not increased. In one case of fracture of the upper part of a femur, which united strongly but with a definite varus deformity, slight changes indicating an early arthritis of the adjacent knee resulted. It was concluded that chronic trauma was a much more likely factor than single acute trauma in producing hypertrophic arthritis.

Synovial Fluid in Traumatic Arthritis. Synovial fluid in traumatic arthritis may be characteristically altered: increased erythrocyte content and icteric index (Forkner, 1930). The finding of a positive Wassermann reaction on synovial fluid should not necessarily change the diagnosis from traumatic to syphilitic arthritis. Bick[6] reminds us of Osler's dictum " Even a syphilitic may have traumatic arthritis."

Treatment. Early vigorous treatment of injured joints may be necessary to prevent chronic disability.[13, 14] This includes rest and the proper type of physical therapy. In some cases physical therapy may give great relief; in others (post-traumatic epicondylitis humeri) rest and splints alone may be indicated. Physical therapy should not be long continued when no benefits are derived therefrom. By treating compensation cases too long physicians may make invalids of them, taking from them the responsibility of getting well and making them rely on somebody else. In such cases physical therapy should be given in a hospital by a physician on a fixed salary, independent in his judgment as to when a patient should be discharged. Professional physical therapy should be supplemented by home physical therapy.

Carruthers [15] reported that early aspiration of synovial exudates in knees was generally followed by early resumption of walking and a good functional restitution. He favored avoidance of weight bearing for a week after aspiration, advising the patient to move his joint in bed, and allowing him to walk with crutches. Bick [6] condemned the routine aspiration of such exudates unless they are persistent.

By applying a "sponge-compression dressing" Forrester [16] avoided the use of aspiration, casts or splints in cases of traumatic synovitis of knees.

A protective cotton pad was placed in the popliteal space and held in place by a circular dressing of sheet wadding. A porous rubber bath sponge was cut longitudinally to fit the contour of the synovial cavity. This was held in place by a gauze bandage. By its gradual expansion as the exudate resorbs, the rubber sponge exerts a constant compression which hastens absorption of the exudate. The bandage is reapplied every four or five days. The exudate disappears in three to six weeks. No edema of the leg occurs and the patient is permitted to walk and work throughout treatment.

Histamine iontophoresis was advocated by Kling.[17] The use of short wave or high frequency diathermy was favored by Bierman and Schwarzschild.[18] Synovectomy [19] and arthroplasty [20, 21] are occasionally indicated.

Stenosing Tendovaginitis at the Radial Styloid. Since its first description in 1895 by de Quervain, about 200 cases of this condition have been reported. The tendon sheaths of the abductor longus pollicis and extensor pollicis brevis are involved in a marked fibrosis of the common sheath in the groove at the lower end of the lateral surface of the radius. Brown [22] recorded a typical case, the third report in English. The condition is regarded of traumatic origin from excessive use of the thumb as in writing, washing, wringing clothes, chopping wood, and so forth.

Brown's patient, a woman aged 62, had a severe constant boring pain in the left wrist at the styloid process. Pain invaded the arm and was aggravated by motion of the wrist, especially of the thumb. Local swelling and tenderness were present. Although roentgenograms are usually negative, periostitis was present. De Quervain's operation is generally advocated for such conditions: incising the tendon sheath under local anesthesia. Operation being refused in this case, a plaster

cast was applied to the wrist and thumb, the latter in full abduction and extension. After 18 weeks the patient was cured. (It is regretted that the diagnosis of stenosing tendovaginitis rather than local periostitis could not have been verified by operation.—Ed.)

Gonorrheal Arthritis and Tenosynovitis

Clinical Data. The clinical features of gonorrhea of articular and periarticular tissues have again been reported.[23, 24, 25] To his previous series of 69 cases presented with Keefer,[2] Myers has added 16 more, reported with Gwynn.[25] Several points are worthy of reëmphasis: Gonorrheal arthritis generally appears within 10 to 21 days after the initial urethral infection, but occasionally may not appear for months or years thereafter. An acute polyarthritis or polyarthralgia was present in 87 per cent of the cases of Myers and Gwynn. An initial polyarthralgia may resolve into a more stubborn monarthritis. A monarthritis alone was present in only 13 per cent of the cases. This is contrary to previous teaching. Knees, ankles, wrists, metacarpophalangeal joints and shoulders are most frequently affected. Fever (to 104° F.) and leukocytosis (to 23,000 leukocytes) are generally present. The sedimentation rate was increased in all of Myers and Gwynn's cases. Certain misconceptions have been that gonorrhea affects the os calcis with spur formation so often that most cases of calcaneal spurs should be considered gonorrheal, and that involvement of the spine, temporo mandibular or sternoclavicular joints is common. Current reports again refute these ideas. Gonorrheal spondylitis is uncommon: of Woods' [23] 70 patients with gonorrheal arthritis, only one had spondylitis. Involvement of a sternoclavicular joint is "unusual" [23]; only two of 85 patients had it.[25] Gonorrheal spurs are rare: seven instances in 85 cases. These observations confirm Von Lackum's contention (1930) that "gonorrheal spurs" is a misnomer.

Gonorrhea tends to affect tendon sheaths: tenosynovitis with arthritis is common. Extensor tendon sheaths of palm and wrist are most commonly affected. Of Myers and Gwynn's [25] patients with gonorrheal arthritis, 48 per cent had tenosynovitis. It occurs without arthritis much less commonly. The incidence of purulent tenosynovitis is reputedly rare: 1 in 7,000 cases of gonorrhea in males. Four new cases were reported by Murray and Morgan,[26] Zadek,[27] and Birnbaum and Callander.[28] The last named reviewed the literature. The tenosynovitis may be acute or chronic. Although severely affected, the tendons are rarely destroyed. Mild subacute trauma precipitated, and conditioned the location of, the attacks in three of the four new cases reported. Involved areas were: the long head of the biceps brachii at the left shoulder, the radial and ulnar bursae at a wrist, and the tendons of a right thumb and those of an index finger. Gonococci were found in smears of pus from two of three cases examined. In Zadek's case, smears and cultures from pus were negative for gonococci, but microscopic examination of the tendon sheaths showed numerous pus cells with intracellular, gram-negative, biscuit-shaped diplococci.

(The patient denied genital gonorrhea. A purulent vaginal discharge was present but smears revealed no gonococci. Gonococcal complement fixation test was negative on the third day of the tenosynovitis. Regardless of these facts the report and photograph seem to warrant acceptance of the diagnosis made.—Ed.)

Surgical drainage was performed in these cases. Functional restitution was generally good.

Complications. In 20 per cent of Myers and Gwynn's cases [25] a catarrhal conjunctivitis was present. Non-purulent in type, it lasted about two weeks. No gonococci were recovered from the scanty mucoid exudate. Iritis was present in 3.5 per cent, ulcerative aortic endocarditis in 2.4 per cent. Woods [23] occasionally noted lymphangitis.

Roentgenograms. Some have asserted that roentgenographic alterations in gonorrheal arthritis are at times highly characteristic if not pathognomonic. Ankylosis between patella and femur, "moth eaten vacuolated areas of decalcification," and "spotty ground-glass atrophy" of juxta-articular bone have been offered as characteristic alterations. The majority opinion has been that such alterations simulated those of other arthritides and were not specific. This was the conclusion of Kapo [24] and of Ferguson, Kasabach and Taylor.[29] A great variety of nonspecific alterations, from simple soft-tissue swelling to diffuse bony ankylosis, was encountered, as should be expected in a disease of such diverse manifestations and variable severity. A clinical diagnosis cannot be ventured by a roentgenologist unless he knows the approximate duration of an arthritis and whether the part has been used. In some cases of acute gonorrheal arthritis of short duration, roentgenograms may resemble those of old tuberculous arthritis. If one is familiar with the time elements in a given case, when a roentgenogram exhibits destructive changes simulating tuberculous arthritis which are known to have developed rapidly (within a few weeks—much faster than is usual in tuberculous arthritis)—such a roentgenogram should arouse suspicions of gonorrhea. Diagnosis must be confirmed by clinical data.

Laboratory Data. Diagnosis and proper treatment of gonorrheal arthritis depend of course on proof that the patient has gonorrhea. It is imperative that physicians be familiar with certain special knowledge: the rather individualized technic of obtaining an honest history, the physical signs to search for and the best method of examination, and the relative significance and reliability of clinical and laboratory data. These matters are reviewed in further papers [30] of the Neisserian Medical Society of Massachusetts.

Isolation of Gonococci. Isolation and identification of gonococci from smears are less accurate than by the new culture method which utilizes "the oxydase reaction" with tetramethylparaphenylenediamine hydrochloride, bacterial growth being enhanced by an atmosphere of CO_2. First described by Gordan and McLeod (1928), the method was modified and extended by McLeod and his associates (1929, 1934). Its value was confirmed by Price (1929) and by Leahy and Carpenter.[31] Thompson [32] simplified the

manner of applying CO_2. By this method gonococci were isolated by McLeod et al. (1934)[2] twice as often as from smears.

(One of us noted the comparable recovery of gonococci by the two methods as done by Thompson: From 175 patients suspected of having gonorrhea, cultures or smears were "positive" in 44 [25 per cent]. In 14 of these 44 cases both cultures and smears were positive; in 30 cases smears were negative but cultures were positive. Cultures have been of great help in confirming suspicions of gonorrheal arthritis. —Ed.)

When synovial exudates were present, gonococci were recovered by Myers and Gwynn [25] from 25 per cent of the exudates. Kinsella [33] found it extremely difficult to recover gonococci from synovial fluid in cases with a copious, thin straw-colored effusion, but found them with comparative ease both in smears and on culture in cases presenting a dense, brawny, exquisitely tender periarticular infiltration and relatively scanty purulent synovial fluid.

Gonococcal Complement-Fixation Reaction. This test on blood is gaining recognition as one of considerable value, one that should become a routine diagnostic procedure.[29, 34] King [35] feels it is as useful in gonorrhea as the Wassermann reaction in syphilis. Myers and Gwynn [25] found it positive in 86 per cent of 43 cases of proved gonorrheal arthritis. McEwen, Bunim and Alexander [29] obtained a positive reaction in 98 per cent of 43 cases. Certain errors in technic and in the interpretation of the test must be avoided. By using a new antigen and a new technic, Price [36] thought the test had been made more dependable and cross-fixation reactions had been excluded. By testing complement both for its hemolytic and fixing powers, irregularities can be avoided, according to Thomson, Hamann and Park.[37]

The reaction is usually negative, rarely positive the first 10 days, and generally becomes positive between the second and third week of infection. A negative reaction may sometimes be obtained if a urethral infection is "open": such a negative test indicates efficient drainage with insufficient absorption of substances to produce the reaction in blood. In such cases a negative test can and does occur even when smears are positive (King [35]). A negative test should also be expected when a patient with gonorrhea is really cured or in non-gonorrheal cases. A weakly-positive reaction should not be considered certain evidence of infection, but if it is repeatedly (weakly?—Ed.) positive or strongly-positive Price [36] concludes that the patient has gonorrhea. Repeated tests are recommended and will prevent diagnostic errors. Tests should always be interpreted in the light of clinical findings. Special caution must be taken to avoid errors in diagnosis when a patient with old or recent gonorrheal urethritis later develops a (coincident) non-gonorrheal arthritis. A positive complement fixation reaction may be present but is unrelated to the arthritis.[23, 29]

Skin Reactions to Gonococcus Filtrate. When Cumming and Bur-

hans [38] gave intradermal injections of gonococcus filtrate (Corbus-Ferry) in the treatment of gonorrhea, the urethral discharge at times increased, as it may with nonspecific protein injections. Local skin reactions at the site of injection included an area of redness surrounding a wheal. Injections of 0.1 to 0.4 c.c. of the filtrate into non-gonorrheal controls produced no skin reaction and no urethral discharge. Cumming and Burhans concluded that both the provocative effect on the discharge and particularly the skin reaction are useful in diagnosis. They thought that the skin reaction was specific because injections of bouillon used in preparation of the filtrate produced no reactions in gonorrheal or other patients.

(The report presents but few details of the reaction. "Several" controls were used. Further information should be forthcoming before one can evaluate the procedure.—Ed.)

Differential Diagnosis. When, as often happens, gonorrheal arthritis begins as an acute polyarthritis or polyarthralgia, shifting rapidly from joint to joint before localizing (if ever) more stubbornly in one joint, its differentiation from rheumatic fever may be difficult as two of Myers' cases illustrate.[39]

A young woman developed acute febrile polyarthritis. Aside from her joints, physical examination was negative. A diagnosis of rheumatic fever was entertained, but salicylates persistently failed to give relief and electrocardiograms were repeatedly normal. Dissatisfied with a diagnosis of rheumatic fever, Myers examined synovial exudate. Gonococci in pure culture were found. The synovial leukocyte count was 58,900 (90 per cent being polymorphonuclear cells). The gonococcal complement fixation test was positive on blood and on synovial fluid. Uterine cervical secretions revealed no gonococci.

A young man developed an acute, febrile migratory polyarthritis five days after an upper respiratory tract infection. The heart was not enlarged. An apical systolic murmur was present, transmitted to the axilla. The second pulmonic sound was accentuated. He had had gonorrhea four and seven years previously and prostatic secretions now contained gonococci. Gonorrheal polyarthritis was considered, but the electrocardiogram revealed partial heart block, a PR-interval of 0.24 second. Aspirated synovial fluid contained 10,450 leukocytes per cu. mm., 88 per cent being polymorphonuclear cells. No gonococci were found in the synovial fluid and the gonococcal complement fixation test was doubtfully positive thereon and on blood. When salicylates were given the fever and arthritis subsided but returned when salicylates were omitted. A presystolic murmur developed. Final diagnosis was rheumatic fever, with rheumatic polyarthritis and carditis and an incidental prostatic gonorrhea.

In the differentiation of gonorrheal polyarthritis and rheumatic fever, these points are important: The value of the complement fixation test and diagnostic aspiration of synovial fluid is evident but results must be carefully interpreted. Prodromal pharyngitis commonly initiates rheumatic fever but is not infrequently seen with gonorrheal arthritis (10 per cent of Myers' 69 cases). Electrocardiographic alterations speak for rheumatic fever, as do response to salicylates and associated involvement of pleura or

lungs. The presence of serous conjunctivitis suggests gonorrhea (it was present in 20 per cent of Myers' cases).

Treatment. Further experience indicates that fever therapy may be the method of choice. For patients for whom fever therapy is not available or is contraindicated other methods must be used. Garland's experience[40] with roentgen therapy in 30 cases of gonorrheal arthritis led him to believe it may be equal or superior to fever therapy. Roentgen therapy is much simpler than fever therapy, which he considers an exhausting "ordeal by fire." Affected joints were given small doses of roentgen-rays twice weekly for two to three weeks. Some patients had previously had foreign protein therapy without relief. Twenty-eight patients (93 per cent) were much improved; two (7 per cent) were unimproved. A total of 80 joints were affected: 30 became symptom free, 45 were "improved," five were unimproved. About 50 per cent of the improved cases appeared to be completely cured within a few weeks after treatment. (This apparently refers to articular lesions: no comments on the primary infection were made.) The remainder improved gradually, became free of pain but had slight articular stiffness or disability. Five patients, certain of whose joints were left untreated as controls, showed no improvement in untreated joints. Garland cited the similar experiences of Akerlund (1930) and of Westermark (1933): the former regarded the effect of roentgen therapy in gonorrheal arthritis as "magical," the latter as better than any other method for gonorrheal hips.

(Garland's report is arresting both because of, and in spite of, its optimism. The matter of controls might seem to have been satisfied by the continuation of disease in untreated joints, but this is not full proof. Garland realized that gonorrheal arthritis is an extremely "labile" form of arthritis, often capable of being rapidly relieved by various remedies or spontaneously by the self-limiting nature of the disease. His comment that in some of the acute cases the relief of pain was "almost theatrical" makes us believe that a transitory arthralgia, not a true arthritis, must have been frequently present. No adequate explanation of the relief is offered, no cultural examination of joints was made, no study of the effects of roentgen-rays on the gonococcus in vitro or in vivo. It is to be regretted that results in this series were not compared with a control series of patients whose joints were treated otherwise, or were untreated.—Ed.)

Three patients "were benefited" with histamine iontophoresis (Kling[17]). Cases of gonorrheal arthritis were among the arthritides that responded favorably to gold salts (Forestier,[41] Slot[42]).

(In these reports few or no details concerning the joints are given; the number of patients treated is quite small and no control series treated by other than the favored remedy is presented.—Ed.)

Gonococcal immunogens, sterile milk, lactalbumin and the intradermal use of stock gonococcal vaccines are valueless according to Cumming and Burhans[38]; but the use of gonococcus filtrate (Corbus-Ferry) seemed to give "specific aid" in the treatment of 124 patients with gonorrhea and its

complications, including arthritis. This filtrate is a soluble toxin and is not to be confused with vaccines (bacterial suspensions), immunogens (bacterial washings), toxoids (solution of formaldehyde detoxified toxin) or serums (antitoxins). Patients generally received 7 to 10 injections, sometimes as the sole treatment, usually as an "adjunct to mild local treatment."

(Results were not statistically presented; no controls were mentioned. Hence evaluation thereof is not possible.—Ed.)

Wolbarst [43] considered gonorrheal arthritis usually secondary to a primary focus in the vesicles for which vasotomy, with the injection of 5 per cent argyrol, is the most effective treatment. In such cases Goldstein,[44] however, opened the vesicles and drained them by perineal exposure. When aspiration of joints revealed serous or serofibrinous synovial exudate, Cooperman [19] used "closed drainage" (aspiration and irrigation). When thick turbid exudate was recovered, "open drainage" by incision was necessary to prevent serious articular destruction. (Some of us believe that even in such cases conservative treatment, aspiration and rest, or fever therapy, is effective.—Ed.) By one or the other method Wolbarst [43] treated 136 gonorrheal joints of 43 infants; to all but 11 joints complete functional restitution was provided. After ankylosis has occurred much can still be done by arthroplasty.[20, 21] To prevent articular and other complications, in view of the local influence of trauma, Woods [23] advised patients with acute gonorrhea to live a sheltered life, preferably in bed temporarily.

Fever Therapy. Sixteen more reports on fever therapy for gonorrheal arthritis have appeared since those mentioned in our last Review (Warren, Carpenter, Boak [45]; Kendell, Webb, Simpson [45, 46]; Tenney [45]; Atsatt and Patterson [45, 47]; Hench, Slocumb and Popp [45, 48, 49]; Bierman, Horowitz [45, 50]; Stecker [45]; Hefke [45, 51]; Arnold [45]; Lepore [45]; Schnable and Fetter [45, 52]; Strickler [45, 53]; Short and Bauer [54]; Wolf [55]). (One of us has published summaries of the literature on this subject to date [Hench [29, 48, 56].—Ed.) Current reports apparently confirm the excellent results noted earlier. It would appear that fever therapy acts almost as a "specific" in the majority of cases of gonorrhea and its complications. Some regard the development of fever therapy for gonorrheal arthritis as the greatest advance of the decade in the field of articular diseases. Therefore, a brief tabular synopsis of reports published from 1932 to 1935, inclusive, seems worthy of presentation (table 1).

Boak, Carpenter and Warren [45] showed that the thermal death time of 130 strains of gonococci in vitro at 106° to 107° F. was about 6 to 27 hours. A patient may be infected with more than one strain. Strains derived from a patient and from his consort generally have the same thermal death time. When a patient exhibits strains whose thermal death times differ markedly, he is probably affected with both an old and new infection. Articular strains are somewhat less resistant to heat than urethral strains; therefore, gonorrheal arthritis may subside before an associated urethritis does.

TABLE I

TABLE I

Results of Fever Therapy for Gonorrheal Arthritis (1932 to 1935)

Authors	Method used	Dosage of fever		Treatments		Number patients treated	Results, per cent				Comments
		Hours each treatment	Temperature (Fahrenheit)	Days interval	Total number		"Cured." Symptom-free	Marked relief	Moderate relief	Little or no relief	
Carpenter and Warren (1932)	Diathermy and radiothermy	5–7	106.7	*	1–2	*	*	*	*	*	"Gonorrheal arthritis usually cured"
Bishop, Horton, and Warren (1932)	Diathermy and heated cabinet	5	106.7–107 (rectal)	*	2	9	*	*	*	*	"Results very encouraging; joints become painless"
Warren and Wilson (1932)	*	5	106.7 (rectal)	*	1–2	2	100				
Warren, Carpenter, and Boak (1935) [45]	*	5–17	106.7 (rectal)	*	1 (equal to thermal death time of patient's strain)	15	87	*	*	*	"Patient may be infected with two strains. The thermal death time of that of patient and consort generally about the same. Strains from urethra and joints may have different thermal death times; usually a little shorter from joints"
Tenney (1932)	Radiothermy	3–4	104–106 (rectal)	*	*	*	*	*	*	*	"Acts almost as a specific"
Tenney (1935) [45]	*	*	*	*	*	3	100				
Berris (1933)	Heated cabinet	2–4	102–103	*	4–6	2	50			50	
Simpson, Kislig, and Sittler (1933)	Radiothermy and heated cabinet	5	105–106 (rectal)	*	*	*	*	*	*	*	"Results gratifying"
Simpson (1934)	Radiothermy and heated cabinet	5	105–106.8 (rectal)	7	*	12	100				"Results uniformly successful in acute cases"
Kendell, Webb, and Simpson (1935) [45, 46]	Kettering hypertherm	6–7	106–107	3–5	4–5	Acute 19 Chronic 12	84 41	* *	* *	* *	

TABLE I—*Continued*

Authors	Method used	Dosage of fever		Treatments		Number patients treated	Results, per cent				Comments
		Hours each treatment	Temperature (Fahrenheit)	Days interval	Total number		"Cured." Symptom-free	Marked relief	Moderate relief	Little or no relief	
Atsatt and Patterson (1933)	Diathermy and heated cabinet	2–6	103.5 (oral)	*	*	Acute 8	88		12		"In failure, temperature given was too low"
Atsatt and Patterson (1935) [46, 47]	Diathermy and hot air cabinet	2–4	104–105	7	1–5	Chronic 1	100				
Kovacs and Kovacs (1933)	*	*	*	*	*	*	*	*	*	*	"Good results even in stubborn chronic gonorrheal arthritis"
Hedrick (1933)	*	*	*	*	*	Acute 1		100			
Jones (1934)	*	*	*	*	*	Acute 10	100				
Hench, Slocumb and Popp (1935) [48, 49]	Kettering hypertherm	5	106–106.8 (rectal)	3–4	3–6	Acute 9 Chronic 7	44 14	56 58	14	14	
Hench (1935) [49]	Kettering hypertherm	5	106–106.8 (rectal)	3–4		Acute 1	100				
Bierman and Horowitz (1935) [48, 50]	General fever: Photothermy cabinet Local-pelvic diathermy electrode	3–4	105–106 (rectal) 111–112 (pelvic)	14	3	2	100				Combined general and local heat (pelvic diathermy electrode)
Bierman (1935) [48, 50]	General fever: Photothermy cabinet Local-pelvic diathermy electrode	3–4	105–106 (rectal) 111–112 (pelvic)	14	3	16	81		6	13	Complete cure if bony changes not present. Physiotherapy for residual stiffness
Stecker (1935) [45]	*	*	106	*	1–2+	18	61		33	6	
Hefke (1935) [48, 51]	Kettering hypertherm	5–6	105–106	*	3	4	100				

TABLE I—*Continued*

Authors	Method used	Dosage of fever: Hours each treatment	Dosage of fever: Temperature (Fahrenheit)	Treatments: Days interval	Treatments: Total number	Number patients treated	Results, per cent: "Cured." Symptom-free	Results, per cent: Marked relief	Results, per cent: Moderate relief	Results, per cent: Little or no relief	Comments
Hefke (1935) [46, 51]	Kettering hypertherm	5–6	105–106	*	3	4	100				
Arnold (1935) [46]	*	*	*	*	*	19	89	11			"Results remarkable"
Lepore (1935) [46]	*	*	106–107	*	*	6	100				
Schnable and Fetter (1935) [46, 52]	Kettering hypertherm	5	106–107 (rectal)	7	2–6	Acute 9 Chronic 9	67 56	22 33	11 11		In acute cases results "striking" to "miraculous"
Strickler (1935) [46, 53]	*	6–7	105–107	*	4	Acute 9 Chronic 4	45	22	22 75	11 25	No better than other treatment
Short and Bauer (1935) [54]	Diathermy	*	*	*	*	*	*	*	*	*	Nearest thing to "specific" ever employed. Results remarkable, but equally favorable results from fever reactions to typhoid vaccine given intravenously
Wolf (1935) [55]	*	*	*	*	*	*	100				"Acute cases all cured"
a. Estimated total (not recounting overlapping series) acute and chronic						182†	About 70	About 15	About 10	About 5	
b. Estimated total of cases presumably acute (those not listed as chronic)						149‡	About 75	About 10	About 10	About 5	
c. Total cases known to have been "acute" (definitely stated)						66	About 70	About 15	About 10	About 5	
d. Total "chronic" cases (more than six weeks' duration)						33	About 30	About 45	About 15	About 10	

TABLE I—*Continued*

* Incomplete data.
† $b + d = a$.
‡ b includes c.

When estimations of the thermal death time are possible, applications of a single session of fever, of a number of hours equal to the thermal death time (generally 5 to 17) at 106° to 107° F., were advocated recently by Warren, Carpenter and Boak.[45] Prompt cure was practically always obtained for those so treated. Good results were also obtained, however, when a period of fever of three-fourths to half the thermal death time was given, suggesting the assistance of defense factors in the body. Since routine estimation of the thermal death time of a patient's strain is not yet practicable, most physicians favor a number of short sessions (as table 1 shows) rather than one long session, but sessions should be given not less than twice a week or strains may become heat resistant.

Various methods for producing artificial fever have included general diathermy, general (as contrasted with local) radiothermy, heated air-conditioned cabinets, hot baths and heated air currents. An analysis of results does not suggest that one is superior to another so far as they affect the disease. A choice of method resolves itself into selection of that one which is most comfortable, least dangerous and least expensive to the patient. The majority favor the administration of 5 to 6 hours at 106° to 106.8° F. (rectal) as one session. Treatments are given every 3 to 5 days. Two to five or six fever sessions are necessary, generally fewer for acute than for chronic gonorrheal arthritis. Statistical data permitted the percentage evaluation of published results in a total of 182 cases of acute and chronic gonorrheal arthritis. Of these 182 patients, 70 per cent (128) were more or less promptly "cured," becoming symptom-free. About 15 per cent more were markedly relieved, about 10 per cent were moderately relieved, and 5 per cent received little or no benefit. Results were definitely better in acute than in chronic cases (over 6 weeks' duration). Of a total of 33 patients with chronic gonorrheal arthritis, about 30 per cent were "cured," about 45 per cent markedly relieved; 15 per cent were only moderately relieved and about 10 per cent were not benefited. Considering the remaining 149 patients to have had acute arthritis, about 75 per cent were "cured," 10 per cent markedly relieved, 10 per cent only moderately relieved and 5 per cent unrelieved. If one chooses to consider as acute only the 66 specifically labelled as "acute cases," the results were still most gratifying and were about the same: 70 per cent were cured, 15 per cent markedly relieved.

Of the approximately 30 reports to date only one is at variance with the others. In Strickler's experience[45, 53] results in 13 cases were no better than with other treatments; nevertheless in his 9 acute cases, 6 patients were cured or markedly relieved. Short and Bauer[54] obtained "excellent results" with artificial (diathermy) fever but obtained equally good results with fever induced by typhoid vaccine intravenously.

(Culver in 1919 noted marked improvement in 22 of 24 patients with gonorrhea treated by fever from intravenous injections of killed colon bacilli, meningococci or gonococci.—Ed.)

These experiences indicate that in cases of gonorrheal arthritis some form of fever therapy should, when possible, be instituted early, but the method used must be able to provide a controllable fever sufficient to reach or exceed the thermal death time of the gonococcus. In cases in which gonorrhea is strongly suspected but cannot be proved, the patient should always be given the benefit of the doubt and be subjected to a couple of trial sessions of fever. If his response is marked, gonorrhea probably was present. Patients who have had arthritis more than six weeks have lost valuable time; but even in chronic cases results may be quite good. However, fever therapy should be regarded as a fire-brigade, not a corps of carpenters; it may extinguish the flames of gonorrhea but will not restore the architecture of the joint. Therefore, when a process is almost burned out except for residual stiffness, fever therapy is not indicated. In two cases of chronic gonorrheal arthritis seen by Kendell, Webb and Simpson,[46] marked stiffness remained after fever therapy alone, but this was relieved by orthopedic manipulation under anesthesia immediately followed by a fever session.

Gonorrhea of the female pelvis is more difficult to cure than this same infection in males. In such cases the combined use of fever therapy and Elliott treatments or pelvic diathermy may be more effective than fever therapy alone (Simpson[45]). Bierman and Horowitz[45, 50] strongly favored the supplemental use of vaginal diathermy electrodes as productive of more local heat than Elliott treatments. Treated by a general temperature of 105° F. by fever cabinet and a vaginal temperature of (not more than) 110° to 111° F. by vaginal diathermy, 37 of 41 patients became bacteriologically "negative" after one to three sessions.

Criteria of Cure. The patient considers his joints cured when symptoms leave; the patient himself is not well until the original focus is also cured. Of 29 patients treated by Desjardins, Stuhler and Popp,[57] 25 were cured after one to 10 fever sessions, "cure" meaning complete disappearance of urethral discharge, symptoms and gonococci in spite of repeated smears and culture, patients remaining free of symptoms for several months. Discharges ceased and smears became "negative" in 9 cases after one fever session, in four cases after two sessions, in three cases after three sessions, in two cases after four sessions and in four cases after five sessions. Three were cured only after seven, eight and ten sessions. King's[35] criteria of cure were essentially similar although he relied considerably on the complement fixation test. In cases wherein treatment was by gonococcus vaccine the test became negative six weeks after patients were clinically cured. However, a negative test is less reliable than a positive test. King believed that when a patient not treated with gonococcus vaccine still presents a positive test even in the absence of symptoms, a persistent focus of infection is undoubtedly present.

(None of these reports included control series of patients treated other than by fever. It cannot be doubted that results from fever are excellent, but fever therapy is a strenuous, expensive, and difficult form of therapy to apply, one which probably

should not become routine in all cases. There are certain dangers in and contraindications to fever therapy. One must remember that articular gonorrhea disappears rapidly and spontaneously in many cases, particularly if "arthralgia" and not true arthritis is present. Even so, under older methods of treatment many cases responded satisfactorily without residue, generally those with serous and not purulent synovial exudate, with involvement mainly in subsynovial rather than synovial tissues,—cases in which the synovial cavity was probably not actually invaded by gonococci (Myers, 1934). Statistics on end-results of older methods are, curiously, difficult to find. Only a few are cited in Mondor's extensive monograph.[58] Complete restitution of articular function was obtained in 50 per cent of Rasch's cases (1916), in 61 per cent of Schüssler's cases (1912). Others noted serious sequelae and articular impotence in at least 30 to 50 per cent of cases (Chiari, 1914). In only 30 per cent of König's and in only 14 per cent of Bodganow's cases (1904), were joints completely cured. Results by older methods depended, of course, on the degree of articular involvement—whether purulent arthritis, or merely a toxic arthralgia or nonpurulent arthritis, was present. Further data on how many cases of each type become healed spontaneously, and how many with treatment recover with or without residue are needed as controls to fever therapy. A more rigid evaluation of fever therapy would be obtained by selecting for treatment only those with positive synovial cultures. However, faced with a method which seems to insure the prevention of complications and a rapid (if strenuous) cure in the great majority of cases of urethral gonorrhea, and early restitution of function in those with arthritis, the matter of selection becomes difficult, and one hesitates to set up controls treated by methods which now seem outmoded. Results in cases of patients so treated, patients unable to afford fever therapy or for whom it is contraindicated, should be carefully compared to those herein tabulated.—Ed.)

General Remarks on Fever Therapy. Fever therapy should not be given in a physician's office. It can be safely administered only in a hospital equipped with specially trained personnel. However, hospitalization after each fever session is generally unnecessary. Physiologic studies have shown that the amounts of fever usually prescribed generally do not harm patients. Hundreds of patients with a variety of diseases have now been so treated. In one series of 400 patients no untoward reactions occurred (Simpson [45]). However, an occasional serious and even fatal reaction is probably inevitable. Only a very few deaths from uncontrolled hyperpyrexia have been reported; four occurred recently of whom two were patients being treated for gonorrhea, one of whom had gonorrheal arthritis.[45, 59, 60] The great majority of patients tolerate the fever quite well but, to prevent such mishaps, physicians and technicians must be familiar with the physiologic reactions to fever therapy, contraindications, management of patients during sessions, and signs of impending trouble as discussed in the references already mentioned. Interesting also are the following references: on physiologic reactions to fever therapy [45, 61, 62, 63, 64, 65]; on immunologic reactions [66, 67]; on various methods used for the production of fever [68, 69, 70]; and on its clinical application and the management of patients.[71, 72, 73, 74, 75, 76]

Short-Wave Therapy. This should not be confused with "fever therapy." In the early development of fever therapy short waves were used to produce the fever by "general radiothermy" or "general short-wave dia-

thermy." Patients received a general, not a local application of the waves. Now, short wave currents are being used to produce merely a local heating or other local effect, not a general fever. In this newer utilization of short waves only local parts, such as joints, are exposed to the waves.

The method is variously called "short-wave" (or "ultra short wave") therapy or "short wave high-frequency" (Schliephake) or "short wave diathermy" (Nagelschmidt), "radiothermy" (Bierman) or "radiathermy" (Kobak). Ordinary or "long-wave" diathermy concerns a wave length of 100 to 400 meters (a current frequency of ¾ to 3 million cycles per second). "Short wave diathermy" (the term approved by the Council on Physical Therapy of the American Medical Association) concerns a wave length of 12 to 30 meters (10 to 25 million cycles per second). "Ultra-short wave diathermy" concerns a wave length of 3 to 12 meters (up to 100 million cycles per second). With ordinary diathermy, heat is produced by conduction; with short wave diathermy heating is due to dielectric losses in a condenser field.[77]

Patients with gonorrheal arthritis were benefited by short wave currents, according to Bierman and Schwarzschild,[18] Kling,[78] Torbett,[79] and Kobak.[80] Kling found reports of 25 patients so treated, with "improvement" in 23. Two of his own patients treated by a 23 meter wave machine also "improved." Of six patients treated by Torbett, 3 obtained "good improvement"; 3 were "moderately improved." One of Kobak's patients with a gonorrheal wrist obtained marked relief from three treatments.

(No details were given in any of these cases.—Ed.)

Several special claims are made for short wave therapy, among them greater and more uniform penetration of heat into the body. With ordinary diathermy superficial tissues are heated more than deep tissues; with short wave currents this thermal gradient is presumably obliterated or reversed. Some have been unable to demonstrate any greater or more uniform penetration of heat than with conventional diathermy.[81, 82] Others, inserting thermocouples into joints and other tissues of animals, observed greater internal (intra-articular) than surface temperatures.[83] Other claims include a specific bactericidal action. Foreign researches suggested that ultra high frequency currents have a lethal action on bacteria, not from a heating effect but because of the peculiarities of the frequency itself. By a process called "point-heating" the temperature of microörganisms is presumably raised above their thermal death point without a corresponding elevation in the temperature of the medium.[84, 85] It is claimed that different bacteria are killed by different wave lengths. These claims are contradicted, however, by several.[81, 86, 87, 88] Gonococci and other bacteria were unaffected by the various wave lengths used and "heatless bacteriolysis" was not noted.

Before short-wave and ultra short-wave diathermy machines are used extensively, their construction must be improved, fire hazards lessened, and more data on their physiologic effects amassed.[77] Using 14 different machines with varying wave lengths from 6 to 25 meters, Mortimer and Beard[82] found no advantage of any one wave length over another for heating purposes.

Tuberculous Arthritis

Clinical Data. Among 12,386 admissions to one tuberculosis hospital were 500 patients with tuberculous arthritis, an incidence of 4 per cent.[89] Joint tuberculosis rarely begins in the capsule. Extension to joints occurs from an adjacent bone lesion. Extension from small bones of the wrists or feet is rapid; that from large bones to adjacent joints may be very slow. Weight-bearing joints are involved much oftener than others. Joints of legs are affected about three times as often as those of arms (Meng and Chen [90]). Of 224 affected joints in Cleveland's cases,[89] 95 per cent were in weight-bearing regions (spine included); only 5 per cent were of upper extremities. In this series the order of involvement was: spine, 49 per cent (especially seventh to twelfth thoracic); knees, 20 per cent; hips, 11 per cent; sacroiliacs, 7 per cent; tarsus, 6 per cent; ankles, 2 per cent; elbows, 2 per cent; wrists, 2 per cent, and shoulders or symphysis pubis, less than 1 per cent. Tuberculosis of the sacroiliacs is particularly serious (Cleveland [89]). It must be remembered that polyarticular tuberculosis is not uncommon. An ankle, knee, elbow and the spine were affected in a case of Slocumb and Ghormley's.[91] Of 100 patients seen by Meng and Chen, 16 had two, four had three, and one had four regions affected. Pulmonary tuberculosis has been reported present in from 6 to 65 per cent of cases of tuberculous arthritis. In the series of Meng and Chen, 47 per cent had pulmonary tuberculosis; an additional 31 per cent had hilus tuberculosis. Of Petter's [92] 45 patients with tuberculosis of a knee, 82 per cent had tuberculosis elsewhere (55 per cent in the lungs). Tuberculous arthritis occasionally first appears after the age of 50 years. Duncan [93] reported two cases in men, aged 67 and 68 years, respectively.

Tuberculous cysts of the knee joint are rare. Elliott [94] reported two cases with multiple cysts proved tuberculous at operation; roentgenographically they were indistinguishable from osteitis fibrosa cystica. In a case of bilateral subdeltoid tuberculous bursitis, Deacon and Ghormley [95] excised bursae filled with rice bodies weighing 100 and 400 gm. Preoperative palpation revealed a peculiar leathery crepitus considered of diagnostic importance.

Roentgenograms. "There exists no roentgen picture entirely typical of tuberculosis in any of its stages" (Sundt, 1931). To this remark Elliott [94] and Doub [11] agreed. Minor variations previously reported [2] as being suggestive of tuberculosis were again noted by Doub. Different roentgenographic aspects of tuberculosis of the knees were diagrammatically presented by Petter.[92]

Treatment. The patient, not just his joint, is tuberculous and the patient's primary disease must be energetically treated. Even at rest, patients may develop bacillemia with new articular and other foci.[92] The use of gold salts is "not quite so successful" in tuberculous arthritis as in tuberculous rheumatism, according to Forestier.[41] (No details were given.—Ed.)

The intra-articular temperature of a tuberculous joint can be elevated to 105° F. by submersion baths.[96] Fever therapy, however, is apparently of no value and may actually harm tuberculous patients. Like physical exercise, fever therapy stimulates metabolism—an effect harmful in tuberculosis. A few patients with tuberculous arthritis were treated and obtained no improvement therefrom (Duncan and Mariette,[45] Huber [45]). Temperatures available in fever therapy do not affect bovine or avian strains, and have no bactericidal but may have a bacteriostatic effect on human strains of *Mycobacterium tuberculosis*. A patient with a tuberculous hip was unrelieved by short wave therapy.[79]

Results of conventional surgical treatment were reported.[15, 89, 97] When ankles were affected by abscesses and sinuses Cleveland [89] advised amputation. He condemned resection of knee joints in childhood since it eventually produces considerable shortening of the leg. The value of the usual orthopedic measures (resection, arthrodesis, osteotomy) has been questioned by Erlacher.[98] Ankylosis is taken for granted as the ideal result. Yet these common practices take years to complete, the tuberculous focus remains and recovery of normal joint function practically never occurs. A purely synovial tuberculosis should be treated by synovectomy before articular bone becomes involved. According to Erlacher, an improved roentgenographic technic indicates that a tuberculous focus in bone almost always begins as a small, isolated circumscribed focus in the capsule or in the region of a joint but not involving it. Early eradication of this focus (by radical extirpation) should be attempted even though rupture into the joint threatens. "The advantage of complete cure at one stroke is so great that one may with confidence assume the risks inevitably involved." Such a procedure is possible, according to Erlacher, in about 25 to 30 per cent of cases, and gives results obtainable by no other method. It allows rapid, firm healing, decreases the duration of treatment a quarter to half, and in many cases preserves normal motion.

Tuberculous Rheumatism

Poncet in 1897 described "rhumatisme tuberculeux" as a condition somewhat resembling acute rheumatic fever with pyrexia, pain and swelling of several joints, leading shortly to frank tuberculous arthritis of a single joint. Others broadened this concept of the disease and advanced the notion that, in some cases, it resembled atrophic arthritis, in others, hypertrophic arthritis, and in still others, juvenile Still's disease. Some believed it due to an actual tuberculous infection with bacilli in joints. The majority, however, have suggested that an atypical tuberculous lesion was present—atypical in that actual tubercle bacilli were absent from joints, the reaction being one of articular allergy to a distant tuberculous focus. Just as there has been no agreement as to the clinical picture of tuberculous rheumatism, so there has been no agreement as to its pathologic or roent-

genographic picture. Hence the condition has been accepted by few clinicians outside of France. In France, however, 12 of 16 "rheumatism specialists" interviewed by Slocumb [99] considered the entity established.

The argument has sharpened since Löwenstein and Reitter (1928) reported that, by a special technic, they could obtain tubercle bacilli in 70 per cent of cultures from blood and synovial fluid of patients who presumably had atrophic arthritis (also from the blood of patients with chorea). Very few have been able to confirm this work (Kallor, 1932) although two French clinicians reported to Slocumb their ability to obtain such positive cultures in 10 per cent of cases of chronic polyarthritis. Criticism of the work of Löwenstein and Reitter was summarized by Tan [100]: a difficult procedure is rendered more difficult by the constant change of method; animal inoculations were not used to determine whether the tubercle bacilli recovered in cultures were virulent or not; bacteriologists who learned the method in Löwenstein's laboratory could not obtain the same results elsewhere.

Criteria considered necessary by some for a diagnosis of Poncet's rheumatism were as follows (Kubirschky [101]): (1) the disease under study should be refractory to salicylates, (2) endocarditis should be absent, (3) non-articular tuberculosis should be present, also, (4) a positive tuberculin test, (5) there should be positive animal inoculation from synovial fluid (some would also add, from blood), and (6) there should be a predominance of mononuclear cells in synovial fluid. In this country and in England the entity has been accepted by very few investigators [102] and rejected by the majority.[103, 104]

Copeman [102] believed that tuberculous foci, at times latent and unsuspected, may be the underlying cause of certain cases now called "rheumatoid arthritis." To support this view two cases were reported:

A 49 year old woman had multiple arthritis of the rheumatoid type following tonsillitis. Her parents had both died of tuberculosis; she had presumably never had it. Sixteen months later, aside from the joints, physical examination, including that of the lungs, was negative. (No roentgenograms of the lungs had been taken as yet.—Ed.) Intradermal tests to old tuberculin and to Parke Davis' "protein purified derivative (P.P.D.)" were strongly positive. No focal or general reaction resulted therefrom. The complement fixation test for tuberculosis was positive, but blood cultures sent to Löwenstein's laboratory were negative for tubercle bacilli. An injection of tuberculin was then given for treatment. A notable reaction followed: fever, malaise, increased arthritis. Râles were then heard at the right apex; a roentgenogram showed possible pulmonary tuberculosis. The reaction subsided in a few days. Three months later the patient had a slight cough without sputum.

In the second case a woman, aged 20 years, had chronic monarthritis of varying intensity in her knee. Two years later the sacroiliacs and the other knee became involved. The next year she was treated (by someone else) for superficial skin ulcers of the legs, presumably tuberculids. Biopsy of the right knee revealed nothing definite for tuberculosis. The next year Copeman found a negative complement fixation test for tubercle bacilli, negative roentgenograms of thorax and knee. The sacroiliacs showed osteitis. Fluid from the knees was negative for tubercle bacilli. Tuberculin tests were positive to both O.T. and P.P.D. Five days later one of the old tuberculid scars became indurated, and four days thereafter an acute exacerbation occurred in

the knees and an ankle. A blood culture, sent to Löwenstein, was positive for tubercle bacilli. The general reaction lasted several days.

(These cases are thought-provoking but not convincing. Results of blood cultures would have been more impressive had they been done, not in Löwenstein's, but in Copeman's laboratory, thus confirming the former's technic. It has long been shown that an exacerbation of atrophic arthritis may follow injections of several unrelated substances, such as milk, typhoid and other bacteria as well as tuberculin. There is therefore nothing necessarily specific about the articular reactions to tuberculin which proves them tuberculous. Furthermore, latent tuberculous foci may also be activated by a variety of substances, not just tuberculin [Hench, 1932]. In tuberculosis such reactions to tuberculin are also not necessarily specific.—Ed.)

Regarding the tuberculous nature of Still's disease very dubiously, Moncrieff [104] cited the observation of Grenet (1935) that positive tuberculin reactions were no more numerous in arthritic children than would be expected in a group of healthy children. Were tuberculosis an important causal factor in chronic polyarthritis or atrophic arthritis, the association of the two diseases should be, at least, not uncommon. Yet among 800 of Dawson's [103] patients with atrophic arthritis only three had (active) tuberculosis. In 4,499 cases of tuberculosis at Saranac Lake, Brown [105] found only 11 cases of atrophic arthritis. Hench [106] restated the conclusion reached by him and Brav (1934) that the existence of tuberculous rheumatism cannot yet be accepted without many reservations.

Although recognizing the insecurity of the entity and the validity of most of the criticism directed against it, Tan [100] cautiously accepted the idea that rheumatism is an allergic disease, a manifestation of articular hypersensitivity to many different bacteria, including tubercle bacilli.

(The few cases presented by Tan as possible examples of "tuberculous rheumatism" seem to us to have been poorly chosen. One patient had for 10 years what we would regard as typical atrophic polyarthritis. Salicylates gave no relief; endocarditis was absent, and residual pleurisy, slight fever, and a positive Pirquet reaction were present. "Animal inoculation" and blood cultures for tubercle bacilli were negative. We cannot therefore see the indications for a diagnosis of tuberculous rheumatism in this case. In another case a patient had pleurisy with effusion and pain and slight swelling of a foot and elbow. Fifteen months later fistulous tuberculosis of the foot developed, tubercle bacilli being found in the discharge and in sputum. The elbow was unchanged. This seems to us like a case of classical tuberculous arthritis, probably of two joints, and not a case of "tuberculous rheumatism." A third patient apparently had had recurrent rheumatic fever and carditis as a child. Some years later miliary tuberculosis developed. Tan considered a possible connection between the two diseases, a connection which seems to us very remote. Two typical cases of Pott's disease were also described, and the case of a woman who had repeated pain and swelling of a shoulder and elbow. At tonsillectomy tuberculous tonsillitis was found. Such cases as these do not clarify the issue; the ever present likelihood of unrelated coincident or subsequent disease being ignored. They strengthen our opinion that to date the syndrome of tuberculous rheumatism rests on insecure grounds.—Ed.)

Slocumb [99] found the treatment of "tuberculous rheumatism" in France to be the same as for atrophic arthritis, except that a few physicians were

using small injections of tuberculin. Forestier [41] used gold salts with reported satisfaction.

Pneumococcal Arthritis

Pneumococcal arthritis is rare. It generally occurs with pneumococcic pulmonary infection (secondary pneumococcal arthritis). Primary pneumococcal arthritis (without a pulmonary infection) occasionally occurs (as it did in 26 of 185 cases of pneumococcal arthritis collected by Plisson and Brousse, 1920). Occasionally a non-suppurative, but generally a suppurative monarthritis is present from which pneumococci can be recovered. Even when the infection is purulent articular function is generally restored and ankylosis is rare. A case of the primary type was reported by Bloomberg [107]:

A 27 year old negress developed fever and a hot, swollen, tender left big toe. Aspiration of the first metatarsophalangeal joint one week later revealed 5 c.c. of thin flaky fluid and fibrin in which pneumococci, type IV, were found. Washed with mercury bichloride, the joint was symptomless four days later. Six weeks thereafter the left ankle and left wrist became involved. Aspiration of the wrist was not done; aspiration of the ankle revealed 15 c.c. of fluid, culture of which was negative. Repeated blood cultures were negative. Roentgenograms of joints were negative. Further treatment consisted of injections of a vaccine of pneumococci and streptococci. Articular restitution was complete.

(Pathological studies were not done. Such studies were recently reported in one case by Allison and Ghormley [1931]—Ed.)

Syphilitic Arthritis and Charcot's Disease of Joints

Syphilis may affect joints directly as a syphilitic synovitis or arthritis, or indirectly as an osteoarthropathy ("Charcot joint") secondary to syphilitic tabes dorsalis. Illustrative of the former, Myers [39] presented the case of a boy "probably with congenital syphilis, with recurrent acute arthritis of both knees":

This boy, an orphan aged 15 years, knew nothing about his family history. At the age of 13 both knees became tender, painful, and swollen for one month and recovered fully under rest alone. Two years later they again became swollen, painful, red and tender. Slight fever and adenopathy were present. Roentgenograms of joints were negative. The Wassermann reaction was positive on blood and on synovial fluid; cultures of joint fluid and the guinea-pig test were negative. Adenopathy disappeared and the joints fully recovered during treatment with neoarsphenamine.

(No diagnosis was definitely given but that of congenital syphilis and recurrent acute syphilitic arthritis is inferred to have been given. The diagnosis of congenital syphilis was apparently based on the idea that the boy was too young to have acquired syphilis. However, no stigmas of congenital syphilis were present and the boy may very well have acquired syphilis. The diagnosis of syphilitic arthritis was apparently made on the basis of the positive Wassermann reaction on synovial fluid and the remission in symptoms coincident with antisyphilitic treatment. These data seem to us insufficient for the diagnosis. Myers admitted "the presence of positive Wassermann reactions on blood and synovial fluid cannot be considered proof of the etiology of the arthritis." Wassermann reactions on synovial fluid of normal joints tend to follow

those on the blood of syphilitics (Forkner, 1930). Had the reaction been negative on blood but positive on synovial fluid, it might have been more significant as far as joints were concerned (Kling, 1932). A diagnosis of syphilitic arthritis should in part rest on the success of antisyphilitic treatment after other treatment has failed. In this case the cessation of arthritis during antisyphilitic treatment suggests, but does not prove the nature of the joint disease. Arthritis may have been incidental, the previous attack having subsided entirely on rest alone. It might be suggested that the patient had recurrent syphilitic synovitis [Clutton's joints], but not arthritis. However, in this condition there is little if any redness, tenderness or pain.—Ed.)

Hypermobility and marked instability of joints are often features of "Charcot joints." Some kind of immobilization is generally required. Cleveland [108] again presented evidence that immobilization by fusion of such joints is possible, though difficult. At first, operation on a patient had produced a pseudo-arthrosis in spite of prolonged postoperative immobilization; later, fusion was successfully accomplished.

Undulant (Malta) Fever: Bang's Disease: Brucellosis

The reported incidence of this disease in the United States is as follows: in 1926, 46 cases; in 1927, 217; in 1928, 649; in 1929, 952; in 1930, 1420; in 1931, 1351; in 1932, 1326; in 1933, 1659, and in 1934, 1787.[109, 110] The increase is believed to be in part a true one and not just due to increased recognition of the disease. Recent experiences with the disease in Tennessee, New Mexico, Iowa, New York (both city and state), Canada and Scotland were reported.[111-116] The disease increasingly presents an industrial hazard to veterinarians, dairymen and meat packers, large numbers (26 to 92 per cent) of whom have it in latent form (Meyer and Geiger [117]).

Bones and joints are commonly affected (50 to 60 per cent of cases [116]), manifestations being arthralgia (migratory, often resembling rheumatic fever), myalgia, non-suppurative or suppurative arthritis, suppurative spondylitis, osteoperiostitis, or osteomyelitis. The general symptoms of irregular prolonged fever, chills, anorexia, sweating, weakness, loss of weight and so on are not specific enough for diagnosis. Recourse must be made to laboratory tests which, however, must be carefully interpreted as their results are variable in different stages of the disease and in different patients. Criteria for diagnosis (Evans, 1934) include: (1) cultivation of the organism from blood or excretions (or joints); cultures often being negative in acute, and more often negative in chronic, cases and most frequently positive in a pyrexial period; (2) positive agglutination test (usually above 1:1000; sometimes only 1:80 or 1:160); however, this may mean only that the patient has had the disease some time; it may be negative even in severe cases, tests in 5 to 16 per cent of cases being negative [118]; and (3) intradermal test with *Bacillus melitensis* antigen (vaccine); this test, however, may remain positive long after recovery, and normal people may develop cutaneous hypersensitivity thereto. Specific and nonspecific cutaneous reactions can be easily differentiated, however, according to Fa-

vorite and Culp.[119] In undulant fever the blood picture resembles that of typhoid fever: leukopenia, lymphocytosis, and during fever a marked left shift of polymorphonuclear neutrophiles.[120] Angle [118] doubted the practicability of Huddleston's test of the opsonocytophagic power of the blood toward Brucella organisms.

New cases with involvement of the locomotor system have been reported.[112, 113, 121-124] Present were: migratory arthralgia or a migratory polyarthritis, a swollen left wrist with osteomyelitis from which Brucella organisms were isolated, and destruction of two or three contiguous vertebral bodies and intervertebral disks in various regions of the spine. (Described as "spondylitis," osteomyelitis was apparently present.—Ed.)

Treatment. When joints are less seriously involved they are treated symptomatically; when purulent lesions are suspected or obvious, aspiration and drainage are desirable both for diagnosis and treatment. Frames and braces may be necessary for spinal lesions (Snyder [124]). For the primary condition many consider the various medicines used (including neoarsphenamine) as of no value.[110, 125] A patient of Ching's [126] apparently responded to neoarsphenamine. Satisfactory response to a triple typhoid vaccine febrile reaction in one case was reported by Beaumont and Page.[127] Transfusions may be helpful.[123] Vaccines of Brucella organisms are of debatable value: some are disappointed with them, others regard them highly.[110, 111, 118, 125, 128, 129] Convalescent immune serum was used in one case with apparent success by Kretzler [130] and Kennan [131] after vaccine had failed. Further experiences with their new antiserum were reported by Wherry, O'Neil and Foshay [132]: 20 patients "responded favorably"; two were doubtfully improved, four unimproved. Failures were believed due to inadequate potency of earlier serums and to insufficient doses. Foshay's Brucella antiserum was recommended by Ashworth and Pickney.[110]

Of interest also are historical notes [109, 111, 118, 133]; studies on the bacteriology [115] and on the immunology of the disease [134, 135]; its experimental production,[136] and its spontaneous occurrence in dogs.[137]

Pyo-Arthroses: Purulent (Septic) Arthritis

As noted, gonococci or pneumococci may produce purulent arthritis. The commonest form of pyo-arthrosis in adults is from gonorrhea. Pyo-arthrosis is commoner in children, when it is generally caused by *Staphylococcus aureus* or hemolytic streptococci, usually secondary to juxta-articular epiphysitis or osteomyelitis. Additional etiologic factors in Veal's [138] cases were abscesses, boils, infected burns, staphylococcal pneumonia, streptococcal sore throat, acute tonsillitis, acute torticollis, and postoperative infection of a popliteal aneurysm; in Inge and Liebolt's cases [139] otitis media, pyelitis and purulent cervical adenitis; in Overton and Meyerding's cases [140-143] a knife stab and a nail wound. The source of infection is often undetermined. Monarthritis is generally present, rarely polyarthritis. A hip or knee is generally affected, less commonly an ankle, elbow, or shoulder.

The usual symptoms are fever, chills, redness, swelling, much tenderness, muscle spasm and articular distention from fluid. It is agreed [138, 139, 144] that although roentgenograms show alterations in joints after a number of days, they are not helpful in early diagnosis so important for treatment if articular function is to be saved. For early diagnosis aspiration of the joints is most valuable and, if the first tap is "negative," should be repeated in suspected cases. One should try to be certain, however, that arthritis and not just periarthritis is present.[141, 143] Insertion of a needle through a purulent periarthritis (as from a stab wound) may infect an otherwise unaffected joint. Cultures of aspirated pus may be negative, possibly owing to the bactericidal properties of synovial fluid.[145] Cultures were negative in 55 per cent of Veal's [138] 68 cases, and in 39 per cent of the 36 cases of Inge and Liebolt.[139] Cultures revealed staphylococci (generally aureus) in 25 per cent of Veal's cases, in 36 per cent of Inge and Liebolt's cases, in 60 per cent of Slowick's [144] 60 cases, and in 100 per cent of Maitland's 8 cases.[146] Streptococci (generally hemolytic) were recovered in 15 per cent of Veal's cases, 32 per cent of Inge and Liebolt's cases and in 39 per cent of Slowick's cases. Other bacteria occasionally recovered were *Bacillus pyocyaneus,* pneumococci, and mixed staphylococci and streptococci.

Three rarer forms of purulent arthritis were reported. A case due to *Micrococcus tetragenus* was reported by Reiman,[147] who found eight such cases with arthritis and two with arthralgia in the literature. Hematogenous osteomyelitis and pyo-arthrosis due to *Salmonella suipestifer* (hog cholera bacillus) were present in the case reported by Weaver and Sherwood [148]; six other cases of such a pyo-arthrosis have been reported. Thirty cases of pyo-arthrosis due to *Haemophilus influenzae* (*Bacillus influenzae* of Pfeiffer) have been recorded, and Peterson reported another.[149]

Treatment. Treatment concerns the patient, the primary focus of infection and the joint. Surgeons of the seventeenth and eighteenth centuries were content to try to save the life of a patient with pyo-arthrosis. In the nineteenth century they tried to save life and limb, ankylosis being a small matter. In the twentieth century the aim is to save life, limb and articular function.[139] All agree that early repeated aspirations or drainage are imperative, but opinions differ on the methods of drainage (simple aspiration, aspiration and irrigation, incision and drainage, arthrotomy). The procedure must be suited to the case under treatment. Amputation is even occasionally necessary.[138, 150] Indications for these different procedures have been restated by several.[19, 138, 139, 146, 150-153] Splints and casts may be necessary.[144, 146] Postoperative physiotherapy and early joint motion are favored by some,[139, 145] used cautiously by others.[138] Of three plans in current favor: (1) drainage and active mobilization (Williams, 1919); (2) drainage, immobilization and traction (Harris, 1925): or (3) joint washing, closure of the joint and temporary immobilization (Cotton, 1916, 1920), Jones [145] favored the third, that is: arthrotomy, washing the joint with physiologic saline solution or with 1:15,000 bi-

chloride solution in saline, and then suturing. Maitland [146] favored the use of proflavine intra-articularly, and euflavine and antistaphylococcal serum intravenously. Staphylococcal bacteriophage for purulent staphylococcal arthritis has been advocated (Rice, 1930, Wiart and Mirallie, 1931; Thiery, 1931). Its value was questioned by Gregoire (1931). Inge and Toumey [154] found it of no value to one patient, and also not helpful in the treatment of experimental staphylococcal arthritis in dogs. Bacteriophage is probably inactivated by body fluids.

Staphylococci are not killed even by the application of 100 hours of heat at 106.7° F. (41.5° C.). Staphylococcal infections would thus seem to be impervious to fever therapy. However, a diabetic patient with an apparently hopeless case of staphylococcal septicemia was reported as having recovered after fever therapy prescribed in desperation (Hartman [45]).

Course and Prognosis; Results of Treatment. The course of pyoarthrosis is limited and not progressive as in "nonspecific infectious" (atrophic) arthritis. Little loss of function may result if treatment is adequate; at other times great destruction and deformity ensue. Arthroplasty and other corrective procedures are later indicated.[20, 152, 153]

Of Slowick's [144] patients, 22 per cent regained excellent joint function, 40 per cent good or fair function. The mortality was 20 per cent in his cases, 18 per cent in Veal's.[138] As the cases of Inge and Liebolt again showed, results are often (54 per cent) good when the condition is not complicated by bone infection, poor otherwise.[139]

Typhoidal Arthritis and Spondylitis

Typhoidal arthritis occurs in 1 to 10 per cent of cases of typhoid fever. Since typhoid fever is becoming rare in the United States, typhoidal arthritis is also becoming very rare, particularly "typhoid spine," one of the less common varieties of typhoid arthritis. No recent reports have been available for our Reviews. Up to 1932, only about 150 cases of typhoid spondylitis were reported (Wang and Miltner, 1932) and only one necropsy recorded (Rugh, 1915). Gambee [155] briefly reviewed the symptoms of the condition and gave 17 references thereon from 1889 (Gibney, who named "typhoid spine") to 1932. In light of newer knowledge of the physiology of the intervertebral disks, Gambee has attempted to explain the pathogenesis of the different varieties of "typhoid spine" and why lumbar vertebrae are particularly affected. Appended was a case report on operative drainage of a vertebral abscess which developed four years after the patient had apparently recovered from typhoid spine:

A boy (age unstated) had typhoid fever in 1929, complicated by empyema and a pararectal abscess. Severe lower thoracic and lumbar backache developed, with fever and muscle spasm, and lasted about three months. A diagnosis of typhoid spine was made (no mention is made of roentgenograms.—Ed.) Four years later, after swimming, low backache, muscle spasm and kyphos developed. Roentgenograms revealed fusion of the third and fourth lumbar vertebrae and partial obliteration of the inter-

vertebral disk, interpreted as a long-standing affair more like typhoid spondylitis than tuberculosis. The Widal test was negative; no typhoid bacilli were found in stools. Leukocytosis (15,750 cells) was present. At operation, an abscess of the affected vertebral bodies and intervertebral disk was drained. On culture the pus revealed a few gram-positive cocci but no typhoid bacilli. The guinea-pig test for tuberculosis was negative. Pain and fever promptly subsided and convalescence was uneventful.

(It is regretted that no report on roentgenograms during the initial fever was given and that the recent roentgenograms were not reproduced. Considering the prolonged viability of typhoid bacilli in the human body (e.g., in the gall-bladder) a diagnosis of "typhoid spine" seems possible, but in the absence of bacteriologic proof the diagnosis is presumptive.—Ed.)

Arthritis with Chronic Ulcerative Colitis

Of 1,500 patients with chronic ulcerative colitis of the type believed due to the diplostreptococcus of Bargen, 60 had coincidental arthritis. Arthritis was the commonest "complication" except polyposis (in 130 cases) and stricture of large intestines (in 110 cases). Bargen [156] and Hench [106] thought that this association cannot be explained satisfactorily on the basis of coincident association of two independent diseases, but that a specific complication and a specific type of arthritis may be present in some of these cases. Analysis revealed four types of relationship: (1) that in which arthritis preceded the colitis by a fairly long time; the arthritis was considered unrelated to the colitis and was generally of the atrophic, rarely of the hypertrophic, type (as chronic ulcerative colitis is a disease of early life); (2) that in which both atrophic arthritis and ulcerative colitis came on more or less together but in which each disease thereafter seemed to progress quite independently, neither being particularly affected by variations in the other; (3) that in which an arthritis resembling atrophic arthritis affected a patient who already had severe ulcerative colitis, but in which exacerbations in joints appeared during remissions, not with exacerbations, of colitis, and (4) the more common type of association—that in which a subacute arthritis appeared with the onset, or more frequently with a subsequent exacerbation, of severe colitis after which the patterns of both diseases showed a striking conformity, remissions and exacerbations of both appearing simultaneously, the joints often being relieved by measures directed to the bowels.

The first two and possibly also the third type of case were believed to represent an unrelated coincident association of ulcerative colitis and atrophic arthritis. The fourth and more common type of case was tentatively thought to represent a specific relationship. One, or several, large or small joints were moderately or severely affected. Periarticular involvement was often more noticeable than intra-articular. Suppuration was not encountered. The appearance and roentgenograms of joints resembled those of atrophic arthritis. In all of these cases the characteristic diplostreptococcus of Bargen was isolated from intestines, and about 80 per cent of the animals injected intravenously therewith were found to have intestinal lesions strikingly like those of patients. However, arthritis was not produced in a single

animal (a significant fact in the face of the presumed ease with which arthritis is produced in animals by streptococcal injections—Ed.). This suggested that the articular lesion in man may result, not from metastatic invasion of the specific diplostreptococcus, but from related "toxins" or an unidentified secondary invader.

Points which seemed to distinguish the arthritic entity were: (1) the clinical relationship between the appearance, activity, and recovery from the colitis and the arthritis; (2) the greater tendency to periodicity and to more complete remissions (at least after earlier bouts) in the arthritis than is usually seen in atrophic arthritis; (3) the striking improvement that may occur in the joints from use of specific serum (antistreptococcic serum therapy for ordinary atrophic arthritis has generally been abandoned as useless); and (4) the fact that although certain streptococci can be isolated from various sites, including the intestines and stools of patients with atrophic arthritis, there were certain cultural and physical differences between them and the diplostreptococci isolated in such cases.

(The foregoing data are admittedly incomplete and inadequate for the establishment of a new entity. Only a few cultures of synovial fluid or tissue have been made as hydrops was not a feature. Cultures revealed no specific diplostreptococci. Pathologic data are not yet presented. Until more information is forthcoming the reader will probably prefer to assume that a coincident and more or less unrelated atrophic arthritis was present with colitis. Those who glibly incriminate more or less symptomless intestines as the cause of atrophic arthritis should note the relative rarity of articular disease in the presence of severe ulcerating lesions of the intestines with blood, pus and multiple stools. Arthritis complicates ulcerative colitis in only 4 per cent of cases, typhoid fever in 10 per cent or less, bacillary dysentery in about 3 per cent, and amebic colitis rarely if ever. Those who "blame the bowels" may find some comfort in the evidence which shows that arthritis and intestinal diseases can be causally related [by hematogenous, not the enterogenous route], but the rarity of a proved relationship should give one pause.

However, there is need for complete open-mindedness on this difficult problem. As many now tend to incriminate symptomless infections of nasopharynx as foci for atrophic arthritis, so some argue that symptomless gastrointestinal infection or "faulty elimination" may play a significant rôle either as a primary or predisposing cause of arthritis.—Ed.)

Rheumatic Fever

Predisposing Factors. A few new data are available on predisposing factors: geography and climate, seasonal influences, social and hygienic conditions, heredity, and the factors of age and sex.

Relation of Geography and Climate to Incidence. Further evidence is presented indicating that rheumatic fever is much less common in the southern than in the northern United States.[29, 157] The incidence diminishes progressively from latitude 50° to 29° (as it does also for scarlet fever but not for acute glomerulonephritis, a fact which is strange [157] if hemolytic streptococci are the cause of each of these diseases). The incidence of mitral stenosis in New Orleans (latitude north 29°) is one-twentieth that in Boston

(latitude north 42°).[29] Either there is much less rheumatic fever in the South or it does not affect the heart as it does in the North. The incidence of rheumatic carditis in two Dallas, Texas, hospitals (latitude north 32°) was low.[158] Of 32,753 medical admissions to a hospital for private patients, 0.34 per cent (114) had rheumatic fever, of which 43 per cent had arthritis, 37 per cent tonsillitis. Only two patients had chorea. Of 10,800 medical admissions to a hospital for charity patients, 1.01 per cent (110) had rheumatic fever, of which 53 per cent had arthritis, 36 per cent tonsillitis. There were two cases of chorea. These figures indicate that rheumatic polyarthritis is less common, chorea much less common, in Texas than in the North.

Rheumatic fever is common in England and Scotland. On a given day in February 1935, there were 99 cases of rheumatic carditis in Edinburgh hospitals: in four large hospitals, one in 8 of all medical patients was suffering from rheumatic carditis (Ritchie[159]). At Queen's Hospital, Birmingham, 4.3 per cent of the 5308 medical admissions between 1924 and 1928 were for rheumatic carditis: these cases formed a third of all admissions for cardiovascular diseases (Brenner[160]).

According to Rogers (1924) and Clarke (1930), rheumatic fever and carditis are practically unknown in the tropics. New statistics refute these contentions. Cairns, Australia, a city of 13,000 people in latitude 17° south, a city well within the tropics, had 666 cases of acute rheumatism in 11 years (Cooper[161]). Mortality statistics from several Australian cities indicate that the severity of rheumatic fever varies with the latitude, becoming progressively greater as one goes from tropical (northern) Australia to the temperate (southern) portion. Usual manifestations of rheumatic fever were present in the cases of Wig[162] in the Punjab (Lahore). According to Kutumbiah[163] 143 cases of rheumatic carditis were seen in three years at the King George Hospital, Vizagapatam, South India, latitude 16° to 20° north—wholly within the tropics. (The clinical data seem quite acceptable. No pathologic data were presented.—Ed.) The report to McKinley[3] from Sprawson, Director General of the Indian Medical Service, indicated that rheumatic fever was to be found generally throughout India. ("The approximate number of cases of rheumatic fever" is given at 276,611—which seems to include cases of "febrile endocarditis" and of "rheumatism." No further explanation is given; the figures cannot be interpreted.—Ed.)

Seasonal Incidence. As elsewhere so in Minneapolis, rheumatic fever in children most commonly appears during early spring (February to April) and late fall (October to December).[164]

Social and Hygienic Conditions. Some think that the poorer the child the more likely he is to get rheumatism: patients studied by Taran[165] all belonged to the poorest class of the community in Brooklyn, New York. Others think it is not the poorest, but the "decent poor," children of the respectable working classes, that are chiefly attacked.[160] The cases of Preston[166] seemed to support this view. In English schools for poor children, rheumatic fever is common, in those for children of the upper classes it is

almost unknown. Eton, a school of 1,100 boys has had only one case in 17 years,[167] but in the town of Eton the elementary school children are frequently affected.[168]

Factor of Heredity and Family Incidence. Rheumatic fever is a familial disease. Whereas Shapiro [164] found it in only 15 per cent of families of non-rheumatic children, he found it in 47 per cent of families of his rheumatic children, often several members of a family having been affected. Among 458 children with rheumatic carditis seen by Gilkey,[169] in the families of 105 children there were two cases, in the families of 20 children three cases, and in the families of 10 children four cases of rheumatic disease. Preston [166] found a familial incidence in 45 per cent of his cases of acute rheumatism with carditis. In his 200 cases Wilkinson [167] found a familial incidence of nearly 70 per cent. However, in a study of 24 patients less than three years of age with rheumatic fever McIntosh and Wood [170] found no simultaneous rheumatic fever in the home and felt that the frequency with which post-rheumatic infection had occurred in the parents of these children was no greater than one would expect to find in any family. (No control figures were given by McIntosh and Wood, however.—Ed.)

Factor of Age. Rheumatic fever and carditis generally first appear between the ages of six and 12 years as current statistics again show. Of Taran's [165] 169 patients, 88 per cent were from six to 12 years of age. The peak incidence of onset was between five and six years in Shapiro's cases,[164] and between 11 and 15 in Ritchie's 244 cases.[159] Rheumatic fever may first appear at any time from birth to old age. Forty cases in infants less than a year old have been reported (Paul, 1932). Although rare under the age of three years, it probably occurs more frequently than is recognized. McIntosh and Wood [170] found references to 40 patients in the first three years of life. In the past 25 years at Babies Hospital, New York City, 24 cases of rheumatic fever affecting children less than three years old were seen. Necropsy was performed in six cases. The impression that rheumatic fever in infants is somewhat different than in older children was not definitely confirmed. Of children less than three years old, 96 per cent exhibited carditis, 46 per cent polyarthritis. However, the clinical picture was "more often that of a general infection than of a specific disease entity." "Several" of Shapiro's patients [164] were less than two years of age.

The disease first appeared, once after the age of 50 years and once after the age of 60 in the cases of Davis and Weiss,[171] occasionally after the age of 60 in those of De Graff, Lingg and Cohn.[172] According to Ferris and Myers [173] when the disease begins in patients more than 60, it is similar to that in younger persons except that polyarthritis is possibly less intense and more persistent. Of six such patients, three died and the characteristic pathologic changes were found at necropsy. Carditis developed in the remaining cases. With appropriate data one should therefore not hesitate to

make a diagnosis of an initial attack of rheumatic fever simply because a patient is more than 50 or 60 years old.

Factor of Sex. Among children, rheumatic fever presumably affects girls more often than boys in a ratio of 6:4. Gilkey's patients [169] with rheumatic carditis included 275 girls, 183 boys. There were 142 females (62 per cent), 85 males (38 per cent) in the series of Brenner,[160] who stated that up to the age of 20 the incidence in males about equalled that in females. The preponderance of affected females begins only after the age of 20 years. Rheumatic carditis is thus less common but more severe in males and gives rise to symptoms earlier. However, in Taran's [165] group of 169 children were 85 girls, 84 boys. Of those with carditis, half were girls, half boys.

General Symptomatology. The familiar and varied symptoms were again described.[159, 167, 170, 174, 175] Many "growing pains" of children are not rheumatic. Differentiations of the rheumatic and non-rheumatic variety were recorded. Rheumatic growing pains, according to Shapiro [164] are commonly articular, affect joints of arms as well as legs, are generally better at night if the patient is warm, worse in daytime and on walking, particularly during the first hour of the day, are often associated with a little fever, articular swelling and heat, and with other signs of rheumatic activity: frequent nose-bleeds, pallor, undernourishment, fever, abdominal cramps and carditis. The non-rheumatic variety are not so generally articular, are usually diffusely and vaguely located in muscles of legs and thighs, appear or are worse at night soon after going to bed, may be gone in the morning, are not present on motion, produce no limping or significant stiffness during the day and are not associated with fever or other evidences of ill health. (Shapiro's differentiation suggests one between arthralgia and myalgia, not necessarily one between rheumatic and non-rheumatic types of pain. —Ed.)

Rather than being better at night, rheumatic pains, according to Rosenblum,[176] may be particularly noticeable at night although they may occur at any time. Non-rheumatic pains in the limbs of the tired, weak child occur only in the legs, often only during or immediately after exercise, and disappear with rest. In case of doubt treatment with salicylates is suggested. "The pains of true rheumatism subside with adequate doses of salicylates."

(There is no reason why many non-rheumatic pains should not also be somewhat relieved by salicylates. The differentiation seems inadequate since the analgesic action of salicylates on rheumatic pain is only relatively, not absolutely, specific.—Ed.)

Rheumatic growing pains may be muscular as well as articular, Preston stated.[166] If muscles of calves, thighs or arms are definitely hard and painful to the touch, they should be considered rheumatic. Many non-rheumatic pains are produced in children by orthopedic defects, which Preston [166] and Elman [177] frequently found in supposedly "rheumatic children." These defects included flat feet, hammer toe, kyphoscoliosis, hallux valgus, hallux rigidus, genu valgum, and pes cavus.

The frequency of tonsillitis and upper respiratory infections as precursors of rheumatic fever has been noted by many. Among 458 rheumatic children Gilkey [169] noted that 70 per cent had had a preceding tonsillitis or recurrent sore throat, and 10 per cent recurrent colds. Respiratory infections occurred as a precursor in 42 per cent of the rheumatic infants in McIntosh and Wood's cases.[170] The reports of Coburn and Pauli are well known; they have further reported [178] that of 17 patients whose throats became infected with an epidemic strain of a toxin-producing hemolytic streptococcus, 14 had a rheumatic exacerbation. Rheumatic fever was often, but by no means always, precipitated by respiratory infections in the cases studied by Bland and Jones [179]: respiratory infections were noted in 75 per cent of those with recurrences. Less than 10 per cent of rheumatic attacks experienced by the patients of Wheeler, Ingerman, DuBois and Spock [180] were preceded within three weeks by respiratory infections.

(Variable opinions on the etiologic significance of prodromal respiratory infections will be discussed later under "etiology and pathogenesis."—Ed.)

Kutumbiah [163] noted that polyarthritis is not nearly as frequent a manifestation of rheumatic fever in children as in adults, at least in the tropics. Of his patients with juvenile rheumatic carditis only 18 per cent had polyarthritis.

Special Symptomatology and Pathology: Cardiovascular. Last year (1935) was the centennial of Bouillaud's recognition of the connection between rheumatism and endocarditis. The course of rheumatic carditis has been again reviewed.[159, 165, 167, 174, 175] In the large cities of the United States about 1.5 to 2 per cent of school children have some cardiac disability. Thus in Chicago about 10,000 children would be so affected.[176] The annual mortality from rheumatic carditis in England is 12,000 to 30,000. Wilkinson [167] estimated that, in England, there are more than 50,000 children and not less than 100,000 adults with rheumatic carditis. Most rheumatic patients develop carditis, particularly infants. Of the latter seen by McIntosh and Wood,[170] 96 per cent had carditis. Newer statistics on the types of cardiac lesions present confirm previous reports.[160, 163, 165, 166, 170, 177] For example, in Brenner's [160] 127 necropsies (with chronic valvulitis) the mitral valve was involved in 99 per cent, aortic in 66 per cent, tricuspid in 19 per cent and the pulmonary in none. According to Brenner, there are three types of cardiac involvement: (1) the acute type, running a fulminating, fatal course without time for chronic valvulitis to develop; (2) the subacute type, with repeated attacks and the development of valvulitis; (3) the chronic type, in which severe carditis never occurs but there are many minor attacks, often entirely overlooked, and in which mitral rather than aortic disease eventuates.

Rheumatic tricuspid stenosis is rare: only 250 cases were reported up to 1933. A case observed by Clemens [181] was unusual because the tricuspid ostium was extremely narrowed, symptoms were those of mitral stenosis, other valves were normal except for mitral insufficiency and slight mitral

valve sclerosis, and the right auricle was only slightly enlarged in spite of the extreme tricuspid stenosis.

Aschoff bodies are rarely found in the myocardium during the first four weeks of the disease; thereafter, they are present in about 90 per cent of cases. An earlier lesion which some believe to be specific for rheumatic fever, may be found—the "fibrinoid degeneration" of Klinge. Chiari [182] reviewed its structure: loosening of interstitial tissue, areas more strongly colored by eosin, and enlargement and irregular swelling of connective tissue fibers—at first with no alteration in nuclei and little or no surrounding cellular reaction. Chiari supported the view that the discovery of such lesions indicates the rheumatic nature of a condition even when Aschoff bodies are absent.

Points in the differentiation of functional and organic murmurs and congenital and acquired carditis were restated by Lyon [174, 175] and by Dwan.[183] An apical systolic murmur, so often found in children, is of no significance unless there has been a recent attack of rheumatism or chorea or unless there is present cardiac dilatation, tachycardia or a lack of response to effort. Maliner's epinephrine test (1932), sound tracings, and microphonic amplification are recommended by Dwan to clarify murmurs.

With rheumatic carditis, pericarditis is not uncommon (about 17 per cent of Brenner's [160] cases). Eight of nine cases of rheumatic pericarditis seen by Antell [184] began during polyarthritis. Cardinal signs are friction rub, an enlarging heart outline, and certain alterations in the left thorax posteriorly: flatness and diminution of breath sounds at the left base, dullness, bronchial breathing, bronchophony and pectoriloquy at the angle of the left scapula. Electrocardiograms were of no aid to Antell in diagnosis. Rheumatic pericarditis alone is uncommon. Yater and Hedley [185] reported the case of a young woman with recurrent rheumatic fever who had pericarditis and septicemia with "alpha prime streptococci." At necropsy, myocarditis and endocarditis were not found. The organisms, injected into monkeys and rabbits, produced arthritis and ulcero-vegetative endocarditis.

Blood vessels are widely affected in rheumatic fever, and Gross and his colleagues [186, 187, 188] have continued their studies thereon. Varied lesions of the coronary and pulmonary arteries, aorta, and the left auricle were depicted in photomicrographs.

Lungs. A clinical diagnosis of rheumatic pleurisy is not often made. The studies of Starr and Parrish [189] indicate that pleurisy is commoner than supposed, as can be demonstrated if routine roentgenograms of the chest are taken during the active phases of rheumatic fever. Interlobar pleural thickening was found in 44 per cent of children with other manifestations of rheumatic fever; it was found in 14 per cent of those with chorea alone but in only 9 per cent of "normal" children.

Nodules. The subcutaneous rheumatic nodule is "perhaps the most characteristic single sign of acute rheumatism." [167] Nodules may appear about joints, especially elbows, knees, carpometacarpal joints, wrists, ankles,

and about the occiput or iliac crests. They vary in size " from a pin's head to an almond," generally that of a " split-pea." They may appear in great numbers or be scanty, especially in infants.[159] (They were present in 14 per cent of Coburn's cases, 1931.—Ed.) In India they are the rarest of all rheumatic manifestations.[163] In Elman's [177] ambulatory cases of rheumatic carditis none were found. Several, unusually large painless nodules were found by Davison [190] in the occipital, iliac and sacral regions of an eight year old boy. After three weeks they receded.

Skin. Erythema annulare rheumaticum, described by Lehndorff and Leiner (1922) is " a specific exanthem associated only with rheumatic endocarditis." It appears following endocarditis, never at the onset of acute fever. Transitory in nature, it is often overlooked. According to Lehndorff and Leiner it occurs in about two-thirds of cases of juvenile rheumatic endocarditis. Abt [191] observed it in six children (more frequently than subcutaneous nodules). The lesions are pale red or bluish-red semicircles or rings one to three cm. in diameter. They are always macular, never papular, and disappear without scaling or pigmentation. They are found on chest, abdomen, back and thorax, rarely on extremities and never on the face or mucosae. There is no itching, edema or hemorrhage.

Exudates. McEwen [192] hoped to find in pleural, pericardial or synovial exudates in rheumatic fever the same characteristic cells which he found (1932) in rheumatic granuloma; however, they were absent. Sixty-two arthritic, eight pleural and five pericardial exudates from 33 patients with rheumatic fever were compared with 35 similar exudates from patients with other diseases. In rheumatic fever there were 800 to 47,000 leukocytes per cu. mm. of synovial fluid, depending on the severity of the arthritis. The cells were nonspecific in character, being similar to those of other exudates.

Routine Laboratory Data (Electrocardiograms, Sedimentation Rates, Blood Counts, Roentgenograms). Each of 63 cases of rheumatic fever seen by Master and Jaffe [193] demonstrated electrocardiographic abnormalities, " unequivocal signs of severe myocardial involvement." Common ones were RST changes (85 per cent), elongation of P–R interval over 0.2 seconds (53 per cent), T-wave inversion (40 per cent), isoelectric T-waves (29 per cent).

(Master and Jaffe did not emphasize sufficiently here or in their previous report (1932) that electrocardiographic alterations may not be seen if only one or two tracings are taken, and that to demonstrate abnormalities in 100 per cent of cases it was apparently necessary to take daily tracings—" as far as possible daily electrical tracings were taken." It is not stated how many single tracings were negative, how soon in relation to polyarthritis the tracings became abnormal, how often only minor abnormalities were present—ones which are sometimes seen in " normal " persons —or the average number of " negative tracings " necessary to be obtained before a case is considered electrocardiographically " negative." Our experience is that single electrocardiograms are frequently negative during the first, or an early, attack of polyarthritis and that in many cases repeated tracings are necessary to obtain some abnormality.—Ed.)

Lead IV, according to Levy and Bruenn,[194] sometimes furnishes evidence of active rheumatic carditis when changes are not observed in the standard three leads; or it may render significant the minor changes in these three leads which otherwise might be regarded as of doubtful importance. Most frequently observed changes in Lead IV were alterations in the direction or voltage of the T-wave.

According to Brenner [160] electrocardiograms are of little use in the diagnosis of chronic rheumatic carditis. Alterations may indicate that some sort of lesion is present, and where it is, but not whether it is rheumatic or not.

Brakeley [195] found that among 100 children with milder degrees of rheumatic carditis electrocardiograms differed little from those found in normal children or those with functional murmurs. They added no information not obtained by physical examination, although they did furnish confirmatory evidence. Important changes to look for in rheumatic carditis are an increased height and breadth of the P-wave, accompanied by notching, increase in the P–R interval, slurring or notching of the QRS complex, inversion of T-wave in two or more leads, and right axis deviation.

The average sedimentation rate at one hour was found by Orme [196] to be 70 mm.

(Westergren's modification of Fahraeus' test was used. Some consider this method too gross to be of value and favor the method of Rourke and Ernstene, 1930. —Ed.)

Leukocyte counts should be done in all cases. Leukemia in children may occasionally present symptoms resembling acute rheumatic fever.[197]

Relation of Rheumatic Fever to Other Diseases.—To chorea. The relationship between rheumatic fever and chorea will be discussed later under "chorea."

To atrophic arthritis. Some believe that rheumatic fever and atrophic arthritis are different diseases, others that they may be different manifestations of the same disease. Dawson [103] and Boots [34] favor the latter view. Similarities are that both show familial tendencies; seasonal incidences are essentially alike; respiratory infections may precipitate either, and subcutaneous nodules of essentially similar type are found in each. There are marked dissimilarities: the age incidences are very different; carditis is rare in atrophic arthritis, common in rheumatic fever. The latter is also characterized by erythemas and by response to salicylates absent in the former. In atrophic arthritis, agglutinins to hemolytic streptococci are present but antistreptolysins are absent; in rheumatic fever the opposite condition obtains.

As evidence of a close relationship Young and MacMahon [198] reported cases in which chronic atrophic arthritis followed what was presumably rheumatic fever and in which mitral disease was present. From a study of pathologic findings in other cases (not these cases) they concluded that articular tissues in either disease presented no definite differentiation.

(The report is open to criticism. Thirty cases were collected, but data on only 10 were tabulated and then so briefly that the reader cannot form his own conclusions. Only two case reports were given and these are inadequate for one to accept the diagnoses given. No roentgenograms, electrocardiographic reports, serologic differentiation or pathologic studies in these particular cases were given. The report seems premature in that no cardiac pathology was available to prove that the carditis was of the true rheumatic variety (with Aschoff bodies, etc.) or of a "nonspecific type." Patients with atrophic arthritis do occasionally develop a nonspecific carditis (Boas and Rifkin, 1924). Patients with atrophic arthritis frequently state that their disease started as an "acute rheumatic fever" or "inflammatory rheumatism." Practitioners are generous with these terms in any acute arthritis, forgetting that acute atrophic arthritis may occur. Careful questioning commonly reveals that acute atrophic arthritis, not acute rheumatic fever, initiated the chronic arthritis. Even were a patient to present pathologic evidence of rheumatic carditis and of atrophic arthritis, it could not be concluded that the two were part of the same disease. One could only conclude that the patient had both diseases, a state of affairs occasionally quite permissible by the law of coincidence or the chances for a double simultaneous infection. —Ed.)

Shapiro [164] believed that juvenile rheumatic fever has little if anything in common with chronic arthritis: "In the hundreds of cases of rheumatic infection which I have followed for the past 12 years I have never seen one instance where the patient developed chronic arthritis directly following juvenile rheumatism."

To subacute bacterial endocarditis. About 4 per cent of patients with rheumatic fever later succumb to bacterial endocarditis (White and Jones, 1928). The majority (50 to 65 per cent) of patients with subacute bacterial endocarditis have previously had rheumatic fever. Ideas as to the nature of this close relationship are that: (1) rheumatic and bacterial endocarditis are reactions of different intensities to the same infection, or (2) subacute bacterial endocarditis is a secondary infection superimposed (a) on old or healed rheumatic valvular lesions, or (b) on recent or active rheumatic vegetations. From a study of 26 cases Von Glahn and Pappenheimer [199] concluded that bacterial endocarditis in rheumatic patients is due to the superficial implantations of non-hemolytic streptococci on active unhealed (not old) rheumatic vegetations. It is not the old scarred valve that is predisposed to subsequent infection with bacteria, but the valve or auricular wall affected by fresh, unhealed verrucae or plaques. Active rheumatic vegetations are a necessary prerequisite to bacterial implantation.

Differential Diagnosis. Rheumatic fever must frequently be differentiated from acute atrophic arthritis, acute polyarticular gout, or acute gonorrheal polyarthritis or polyarthralgia. Master and Jaffe [193] compared electrocardiograms in 63 cases of rheumatic fever and 50 cases of acute atrophic arthritis. In those with rheumatic fever significant electrocardiographic abnormalities were found in 100 per cent (when daily tracings were taken). In those with acute atrophic arthritis there was a complete lack of electrocardiographic evidence of myocardial disease. Thus the presence of a definite abnormality in a given case would speak for rheumatic fever.

(Master and Jaffe have accepted the criticism that the presence or absence of an abnormal electrocardiogram may have influenced them in making a diagnosis of one or the other disease, and admitted a recent tendency to do this but believed that the differentiation was accurate none the less. Before one can establish the practical value of this differentiation further data should be forthcoming, particularly on how early in the disease and after about how many tracings the electrocardiographic abnormality becomes apparent. The paying patient of moderate means cannot afford many serial electrocardiograms, and, as mentioned before, single tracings are frequently negative in the early stage of acute rheumatic fever when differentiation is most desirable.—Ed.)

The early polyarthritic or polyarthralgic phase of gonorrheal rheumatism is often mistaken for rheumatic fever. Furthermore, a patient with chronic gonorrheal urethritis may develop rheumatic fever, the latter being regarded as gonorrheal polyarthritis. In such cases Myers [39] and Boots [34] base differentiation on the electrocardiogram, a positive or negative salicylate effect, bacteriology and cytology of synovial fluid, and the gonorrheal complement-fixation test.

An initial attack of rheumatic fever may occur after the age of 50 or 60 years. However, the commonest form of acute arthritis in males more than 40 or 50 years of age is from gout, according to Hench.[49, 106] It is commonly misdiagnosed rheumatic fever. The stage of acute rheumatic polyarthritis is usually considerably longer (20 to 50 days) than that of gout (7 to 20 days). The diagnosis of rheumatic fever should not be dismissed simply because a patient is more than 50.[173] Differentiation is made on electrocardiographic evidence, estimation of the blood uric acid, effects of salicylates or colchicine, and on the clinical course.

Course and Prognosis. The course and prognosis of rheumatic fever are almost entirely that of its cardiac component. The course is generally one of remissions and exacerbations, with occasional arrest, but usually with a more or less relentless progression. Exacerbations are so frequently precipitated by respiratory infections that some regard the latter not as nonspecific precipitating factors but as an integral part (indeed the specific beginning) of either the first or subsequent attacks. Other factors, however, will provoke attacks: tonsillectomy, severe injuries, injections of typhoid vaccine, or an abdominal or other operation.[200] Bland and Jones [179] noted an initial, generally a subsequent, attack after tonsillectomy, appendectomy, or arthrodesis. Intravenous injections of typhoid bacilli have been used in the treatment of the disease. To study the effect, Bland and Jones gave a total of 12 such injections to 10 patients. In six cases an exacerbation appeared immediately or within three weeks. In two cases there was a doubtful, in four no, reaction. No serious effects were noted. Following the reactions "there seemed to be a more rapid progression to quiescent rheumatic fever than was previously noted." Studying the immunity mechanism, Coburn and Pauli [178] performed splenectomy on 20 children with quiescent rheumatic fever; in nine of these 20 cases recrudescences developed as a direct sequel to splenectomy; none died.

Effect of Pregnancy. With others Willius [201] believed that in many cases of rheumatic carditis the stresses of the latter months of pregnancy, of actual labor and those incident to the subsequent physical care of the infant may precipitate cardiac decompensation. However, trouble does not always develop. Of 38 rheumatic women seen by Brenner [160] 15 had no trouble with repeated pregnancies up to 10. Four had no trouble with one or more early pregnancies, but heart failure developed after later pregnancies. In 19 cases heart failure began or became worse in the first pregnancy; four patients died within a few weeks of delivery.

Evidences of Activity or Reactivity. The following are considered evidences of activity of the disease: the usual clinical evidence of slight persistent fever, tachycardia, joint pains, nodules, persistent underweight, pallor, unexplained abdominal pain, nosebleeds, tendency to vomit, leukocytosis, lassitude, an increased sedimentation rate, and electrocardiographic alterations.[164, 176, 202, 203] The disease may be active, however, without fever. If in the absence of fever the sleeping pulse rate is about the same as "the alert rate" (when the child is awake), activity can generally be presumed. A recrudescence is often evidenced by gradual quickening of both sleeping and alert pulse rates. On the other hand, if a drop of 10 to 20 beats per minute during sleep is noted, a rapid alert rate is probably of nervous origin.[176]

Recurrences. Of Shapiro's [164] 342 patients, 52 per cent had only one attack within the period of study (12 years or less), 48 per cent had one or more recurrences. Of the latter, 27 per cent had them within one year, 54 per cent within two years, 70 per cent within three years, and practically all within nine years. Of Gilkey's [169] 458 patients, 49 per cent had recurrences within three years. Of Preston's [166] 157 patients with carditis 30 per cent had one attack only, 38 per cent had one relapse, 32 per cent had two or more relapses. Of those without carditis, 70 per cent had one attack, 24 per cent had one relapse, 6 per cent two or more.

End Results. The course of rheumatic carditis has been outlined by De Graff and Lingg [172] who studied 644 patients who died of it. Fifty-six per cent were males, 44 per cent females. Rheumatic carditis usually existed alone (95 per cent of cases), was seldom combined with other etiologic types (5 per cent). The average patient is infected at the age of 17 years, but will be free of symptoms and able to carry on ordinary physical activity for 11 years. He will then begin to suffer from diminished cardiac reserve, culminating in heart failure two years later. From this time until his death, three years later, he is wholly an invalid, or at least in most cases is seriously incapacitated. The period of economic usefulness of a rheumatic victim is generally less than nine, not more than 11, years after the initial rheumatic infection. Once symptoms of cardiac insufficiency appear, heart failure and death rapidly ensue. Fifty per cent suffer their first symptoms and failure and die within a period of from 16 to 20 years after initial infection (or

between 20 and 40 years of age). To see even terminal stages of the disease in patients more than 50 years of age is uncommon. Death usually occurs from heart failure, but life is shortened in some cases by subacute bacterial endocarditis, pneumonia and other diseases. Of the 644 patients in De Graff and Lingg's series, 43 per cent developed auricular fibrillation, but this did not per se determine prognosis on life expectancy. When fibrillation, a late manifestation, set in, the die was already cast. The incidence of the various valvular lesions was given. Mitral disease was more frequent in women, aortic disease in men. The location or number of valves affected did not seem to influence the duration of life except in the case of pulmonic or tricuspid valves: then the prognosis was less favorable.

A similar study of 113 cases was made by Davis and Weiss.[171] After the onset of the disease, the patients lived from a few weeks to 40 years. About 50 per cent lived less than six years: about 50 per cent lived from six to 25 years.

Etiology and Pathogenesis. Arguments on various theories are essentially similar to those reported in previous Reviews.

Infectious Theory. Evidence supporting this theory is direct and indirect. Presumably direct evidence is that from cultures of the blood, nasopharynx and other tissues. Blood cultures by McIntosh and Wood[170] were negative in six cases, positive for non-hemolytic streptococci in one. As already noted, the frequency with which tonsillar or upper respiratory infection occurs as a precursor of rheumatic fever has again been demonstrated by Coburn and Pauli,[178] Gilkey[169] and McIntosh and Wood.[170] The significance of this prodromal infection is debated. In Bland and Jones' series[179] of "over 1,200" rheumatic children and adolescents, respiratory infections were experienced by 75 per cent of those with recurrences. However, many exacerbations occurred without preceding respiratory infections and recurrences were frequently precipitated by other and nonspecific factors such as accidents, abdominal operations, or injections of typhoid vaccine. Bland and Jones therefore concluded that the bacteria causing respiratory infections may not be as specifically related to the disease as some believed, but may be of secondary importance.

Of rheumatic attacks among 222 patients of Wheeler, Ingerman, DuBois and Spock[180] less than 10 per cent were preceded within three weeks by a respiratory infection. When such infections did develop, only 16 per cent of them produced rheumatic activity. Practically all of another group of 123 patients suffered respiratory attacks on an average of five each. Although 54 per cent of these infections were with hemolytic streptococci, 84 per cent were not associated with rheumatic activation. A comparison of 4867 throat cultures from 123 rheumatic, and of 1231 cultures from 109 nonrheumatic, children by Wheeler, Wilson and Leask[204] showed no significant difference in the frequency or in the appearance time of hemolytic streptococci and no noteworthy difference in the incidence of such organisms

in throats during apparent health, upper respiratory infections or rheumatic activity. These authors concluded that an etiologic relationship between rheumatic fever and respiratory infections with hemolytic streptococci was not evident.

This conclusion is at variance with that of Coburn and Pauli [178] who distinguished between respiratory infections with non-toxin producing hemolytic streptococci, ineffective in provoking rheumatic exacerbations, and those with a strong, skin toxin-producing hemolytic streptococcus capable of activating rheumatic processes. In the winter of 1934, the throats of a group of rheumatic children were infected with the former type—a non-toxin producer: in none did an exacerbation develop, nor did any during a subsequent influenzal epidemic. Soon thereafter these same children were exposed to an epidemic of a toxin-producing hemolytic streptococcus of a single type. Of 16 rheumatic children thus affected, 14 had acute rheumatism, two escaped. The 14 affected patients developed increased antistreptolysins with the onset of symptoms. The two who were definitely infected with the same toxin-producer but escaped a rheumatic exacerbation did not develop antibody (antistreptolysin) response. Seven rheumatic children did not contract the toxin-producing streptococcal infection, thus indicating that some susceptible persons may live in close association with an epidemic of acute rheumatism, develop no rise in antistreptolysins and maintain excellent health. An additional patient, one with congenital heart disease, did become infected with the "effective strain" and did develop a typical antibody response; yet this patient escaped rheumatic manifestations, indicating that more than a bacterium is responsible for the disease. Cultural characteristics of the effective and non-effective strains were essentially similar, but the effective strain was capable of producing strong skin toxins and streptolysins and was indistinguishable from scarlatinal strains of hemolytic streptococci.

Indirect evidence for the infectious theory is derived from skin tests, and tests for streptococcal agglutinins, antifibrinolysins, streptococcal complement, antistreptolysins and precipitins. *Skin tests* with hemolytic streptococci were "positive" in 80 per cent of Gilkey's [169] 458 rheumatic children and in 20 per cent of controls, and in 75 per cent of Kaiser and Keith's [205] 200 rheumatic children and in 32 per cent of their non-rheumatics. They were also positive, however, in a fairly high percentage of patients with other streptococcal infections.

Agglutinins. Blair and Hallman [206] found a somewhat larger percentage of high agglutinin titers with serums from cases of rheumatic fever than has been reported by others. Twenty-five serums from 24 patients were tested: agglutinins to Cecil's typical strains of hemolytic streptococci AB 66 (from a patient with atrophic arthritis) and Q 33 (from a patient with rheumatic fever) were found in dilutions of 1:160 or more in 14 serums. Only one patient with rheumatic fever had agglutinins (1:40) to *Streptococcus viridans.*

The streptococcal complement-fixation test was positive in varying degrees in Coburn and Pauli's active cases of rheumatic fever (1932), but was only occasionally positive (sometimes strongly) in quiescent cases. Beck and Coste [207] found the test positive for only seven of 79 patients with various types of rheumatism or arthritis, presumably streptococcal: it was positive in two of four cases of rheumatic fever, but also often positive in cases of pregnancy and of tuberculosis.

Antifibrinolysins. Broth cultures of hemolytic streptococci (but not of other organisms) of human origin rapidly liquefy the fibrin clot of normal human plasma. In patients convalescent from acute hemolytic streptococcal infections (and rheumatic fever) the fibrin clot is highly resistant to this fibrin-lysis owing to the presence of a substance (antibody) called "antifibrinolysin." Although certain amounts of antifibrinolysin are found in the plasma of normal persons and those without evidence of recent hemolytic streptococcic infection, Myers, Keefer and Holmes [208] found much greater amounts in plasma of patients with erysipelas and other acute hemolytic streptococcal infections and with rheumatic fever. (However, antifibrinolysins were not found in cases of atrophic arthritis.—Ed.)

Precipitins. Extending previous work (Coburn and Pauli, 1932; Schlesinger and Signy, 1933) Schlesinger, Signy and Payne [209] demonstrated precipitins to hemolytic streptococci in the blood of non-rheumatic patients with recent tonsillitis, but in greater amounts in that of rheumatics. Precipitins are practically absent in cases of quiescent rheumatic fever; in rheumatic patients, they generally appear between the tenth to thirtieth day after the acute throat infection. Just at this time rheumatic relapses commence. Apparently when immune responses are at their height, the patient's tissues seem to possess a vulnerability that perhaps allows an as yet undiscovered cause of rheumatic fever, perhaps a virus, to enter the body or, having already entered, to become active.

*Antistreptolysins.** The normal level of antistreptolysins is from about 50 units [178] to 100 units.[206] Blair and Hallman [206] found increased antistreptolysins in 15 of 18 rheumatic patients. The disease was "inactive" in the three whose titers were normal. Coburn and Pauli [178] found a marked increase in antistreptolysins (to an average of about 500 units) in rheumatic patients infected by the "effective strain" of hemolytic streptococcus; the increase was coincident with onset of symptoms of rheumatic activity. Unless such a rise appeared, no rheumatic exacerbation was experienced. Apropos of the reported rarity of rheumatic fever in the South as compared to the North, Coburn and Pauli [210] found that high antistreptolysin titers are more prevalent in latitudes over 40° than in those below 35°. However,

* Coburn, Wilson and their colleagues use the terms "antihemolysin" and "antistreptolysin" synonymously, but prefer the term "antistreptolysin" which emphasizes the relation of the antibody to streptococci.[212] To be absolutely correct one should use the term "antistreptohemolysin." The antigen, streptolysin, is a soluble product of hemolytic streptococci which hemolyzes erythrocytes. The antibody, antistreptohemolysin or "antistreptolysin," neutralizes the antigen streptolysin; one titrates with streptolysin to determine the presence and titer of "antistreptolysin."—Ed.

the work of these investigators is again at variance with that of their fellow townsmen, Wilson, Wheeler and Leask.[211] The latter made clinical, bacteriologic and immunologic studies on 80 rheumatic subjects over a period of 12 to 18 months. The average antistreptolysin value was 135 units for those with inactive disease; the range was 25 to 715 units. The range among patients with inactive or active rheumatism or with respiratory infections was about the same. Those with respiratory infections unassociated with hemolytic streptococci showed a higher average titer and a greater rise than those with hemolytic streptococcal respiratory infections. An increased titer therefore does not necessarily indicate a hemolytic streptococcal infection. Rheumatic activity developed in many cases without preliminary respiratory infection: two-thirds of them had no rise in antistreptolysin titer. A rise in antistreptolysins is therefore not a necessary accompaniment of rheumatic fever. Increased antistreptolysins seemed directly related to the extent of the local and constitutional symptoms of the respiratory infection, irrespective of the presence of hemolytic streptococci and bore no relation to the clinical course of rheumatic activity.

Interpretation of Immunologic Data. (The work of the Columbia group seems to be in sharp contrast with that of the Cornell group. The writings of the former seem to us easier to follow, although the work of both groups appears to have been done very carefully and exhaustively. It was impossible for us to interpret these immune responses or to harmonize the conflicting views. In an attempt to do so the editors wrote Drs. Wilson, Coburn and Pauli. A possible explanation was offered by Dr. Wilson. She and her colleagues included non-rheumatic children among their controls. Coburn and Pauli apparently did not. Antistreptolysin values for babies approximate those for adults, but those for children may not. Because children are so susceptible to respiratory infections they may, even after minimal infections, have values higher than adults or babies. Rheumatic fever in childhood may be an entity not entirely comparable to that in adults. A further factor may have been the selection of cases for study: there may have been less selection of those of Wilson and her colleagues who included records of all cases seen in a specified time. Since high antistreptolysin titers were noted in patients who did not develop rheumatic exacerbations Wilson was inclined to doubt the importance of a special, potent strain of hemolytic streptococcus. Obviously, final interpretation must await more data thereon. However, the preliminary interpretation of Coburn and Pauli [178] is given.—Ed.)

Three factors seem to be necessary for the production of a rheumatic attack: (1) infection, not just with any hemolytic streptococcus but with a highly effective agent—a strong soluble-toxin producing hemolytic streptococcus, (2) a disease pattern peculiar to each rheumatic subject, (3) an intense immune response as indicated by a rise in antistreptolysins. A patient can be infected with an "effective strain," but unless a marked antibody response develops, a rheumatic exacerbation does not ensue. Therefore, the character of the antibody response plays a large part in determining whether an attack will follow. If the patient's antibody-producing tissue is quiescent when the hemolytic streptococci or other precipitating agent acts (for example, an operation such as splenectomy), no rheumatic exacerbation ensues. If the antibody-producing tissue is in a state of activity at that

time, an exacerbation may result. (To this extent, then, the patient is as much, if not more, the cause of the disease than the invading substance.—Ed.) Thus the pathogenesis of rheumatic fever is presumably as follows: (1) the toxin-producing hemolytic streptococcus initiates a process peculiar to rheumatic subjects; (2) in the course of the process a substance is released presumably from the antibody-producing tissues, which directly or indirectly alters mesodermal structures; this substance is probably not the infecting organism, and at present there is no evidence to suggest that it is viable, and (3) the release of this toxic substance seems to occur only when there is an immune response to hemolytic streptococci.

Coburn and Pauli's idea of a more or less specific sensitivity or allergy, a peculiar antigen-antibody reaction involving a special type of hemolytic streptococcus, is in contrast with that of Swift [29] and others that rheumatic fever results from a hypersensitivity to a wide range of streptococci or other bacteria. The idea of a broad streptococcal allergy is accepted by many.[159, 160, 213, 214, 215] In support of the allergic theory various tissue reactions, including some resembling those of rheumatic fever, were produced by Chiari [182] in animals given allyl-formiate, by Baker, Thomas and Penich [216] in animals sensitized to beta hemolytic streptococci, and by Andrei and Ravenna [217] in animals sensitized to arthrotropic streptococci. However, not all of the animals presented these reactions, and many of the reactions were considered quite nonspecific, unlike the lesions of rheumatic fever.

Objections to the idea that the disease represents general allergy have been raised by Stuart-Harris [218] and by Sayle.[219] Objections are that: (1) the percentage of skin reactions to hemolytic streptococci is no greater in rheumatic than in control groups, and is much less than in scarlet fever; (2) skin reactions to non-hemolytic streptococci are present in rheumatic fever but also in controls; (3) there are many diseases due to hemolytic streptococci and other organisms, to which candidates for rheumatic fever should be sensitive, which are not associated with rheumatic-like manifestations; (4) certain "skin-positive rheumatic patients" with hemolytic streptococci in their throats escape relapses, and (5) in artificial sensitization, the silent period between resensitization and symptoms becomes less and less; in rheumatic fever it remains about the same in spite of repeated exacerbations.

The frankest objections are those of Freeman,[220] who criticized the whole idea of bacterial allergy in rheumatism, particularly the chronic types. In the first place "allergy" is at present a non-definable term, even authorities being troubled by its ambiguity and the difficulty of using it with precision. The types of streptococci, the germs presumably most concerned with bacterial allergy in rheumatism, are not yet satisfactorily classified. Skin tests afford little or no assistance and are quite inadmissable as evidence for "allergy" because their results are so inconclusive: in rheumatism the reactions vary greatly in intensity and time of appearance (four hours to four

days). They do not appear after five to 10 minutes as do the characteristic "wheal" reactions of "allergic diseases" like hay fever. Reactions may also occur in non-rheumatic persons and are not characteristic either of the disease under study or even of the organisms used therefor. Various immunologic reactions reported are not clear-cut because the antigenic properties of the responsible streptococci are adaptable, not fixed. One must strictly differentiate between (1) a specific infectious disease with allergic phenomena (as in tuberculosis), and (2) an "allergic disease" of the sort usually characterized by paroxysmal attacks, as in asthma, hay fever, etc. Aschoff would say, allergic phenomena are present in rheumatism, but rheumatism is not an allergic disease. This does not help us, however, to understand rheumatism. "The use of the word, 'allergy' will help only in so far as it emphasizes the action of the dissolved products of invading microorganisms (rather than the whole organism itself) and the necessity for immunization and desensitization. . . . We are inclined to believe that so beautiful a word as allergy must mean something important without concerning ourselves too much as to what that something may be. . . . We are working in a fog and have as yet no clear vision. The word allergy is, to my mind, not a gleam of sunshine breaking through, but an extra wisp of fog."

Virus Theory. In some ways rheumatic fever resembles a virus disease (Sayle [219]). In certain diseases the virus apparently enters the body via the nasopharynx; a nasopharyngitis precedes rheumatic fever. Some virus diseases predispose to recurrences, which is the case in rheumatic fever. Virus diseases generally have a long inoculation period (nine to 24 days); the "silent period" in rheumatic fever is about 10 to 21 days. Viruses are difficult to grow and are generally ultramicroscopic; were a virus responsible for rheumatic fever, current failures to grow or see it could be explained. In some virus diseases intracellular inclusion bodies are demonstrable; they have not been found in rheumatic fever, although granules of an unknown nature have been found within tissues by certain stains.

Schlesinger, Signy and Amies [221] isolated from the pericardial fluid of seven patients and from the pleural exudate of one patient particles which resembled virus elementary bodies. Suspensions of these bodies were specifically agglutinated by serums of patients with active rheumatic fever, but were not agglutinated by that of normals or of patients with inactive rheumatic fever or with various non-rheumatic infections. Coles [222] recovered similar "virus-like bodies" from pericardium and pericardial exudate of a victim of rheumatic fever (also from synovial fluid in four cases of atrophic arthritis).

(Proof of the significance of these bodies lies in the reproduction of the disease when they are injected into animals. This has not been done by any of these workers. —Ed.)

Theory of Nonspecific Infection Plus Vitamin C Deficiency. Supplementing work with Mettiher and Connor (1934), Rinehart [223] presented fur-

ther work in support of his idea that rheumatic fever may be the result of the combined influence of deficiency in vitamin C and infection. In guinea-pigs on a diet devoid of vitamin C which were inoculated with a guinea-pig strain of hemolytic streptococcus or other organisms, cardiac and articular lesions, and occasionally subcutaneous nodules, notably resembling those of rheumatic fever, developed with considerable frequency. Guinea-pigs infected with these organisms but on an adequate diet did not show such lesions, and those treated with a deficient diet alone showed only slight lesions. Swift [29] agreed that lesions of some sort were thus experimentally produced, but thought they were scorbutic, not rheumatic. He and his colleagues [224] found no difference between rheumatic and non-rheumatic patients in the metabolism of vitamin C. Patients with active and quiescent rheumatic fever were treated with cevitamic acid (concentrated vitamin C). The course of the disease was uninfluenced. Faulkner [225] also noted no definite effect from feeding a high-vitamin C diet in 27 cases of rheumatic fever.

Perry [226] applied the Harris-Ray test for vitamin C deficiency (urinary excretion of ascorbic acid after the administration of a test dose of vitamin C) to five patients with active and six with quiescent rheumatic carditis. Two of the former and three of the latter gave evidences of a mild vitamin C deficiency. However, the capillary resistance test was normal in all five. It was concluded that mild degrees of vitamin C deficiency are not uncommon in rheumatic children but are not important in the etiology of acute rheumatism.

Warner, Winterton and Clark [168] found a much higher consumption of fresh fruits and vegetables by rheumatic children and their families than by children in institutions in which there was a very low incidence of rheumatism. Although the consumption of animal protein and dairy products was low and that of carbohydrates high in the rheumatic group, no one dietary factor could be found as a contributory cause for the disease. Extra feedings with vitamins A and D proved of little value.

Treatment.—For the general disease. Ritchie [159] ascribed no curative value to any serum, vaccine or medicine, including salicylates. The majority ascribe to salicylates only an analgesic effect, and no power to prevent or modify carditis. Citing reports on their ineffectiveness in preventing carditis and on their occasional toxic effects, Apfel [227] stated that the use of salicylates is continued " simply because it has been handed down to us and we don't know what better to use." That salicylates are a specific is a "pernicious doctrine," according to Eason [228] who considers doses now used sometimes dangerous. Others do not approve " the current fashion of belittling the use of salicylates." Antell [184] still regards them as " the sheet anchor " of treatment, even if they are not specific and are only analgesic. He prescribes them in large, " almost toxic " doses: for children, 60 to 120 grains in 24 hours with sodium bicarbonate. Taussig [202] prefers aspirin

to sodium salicylates, considers 30 to 45 grains daily sufficient, and 10 grains of salicylate per 10 pounds of body weight as a maximal daily dose for most children. Wilkinson [167] and Lyon [174, 175] believed that inadequate doses are generally given and that, when enough is used, the drug does definitely prevent or modify the carditis in some cases. To prevent acidosis Lyon prefers "salicionol," an alkalized salicylate.

Replacing salicylates, amidopyrine is favored by Apfel,[227] neocinchophen (tolysin) by Poynton.[229] Fraser [230] saw an instance of fatal cinchophen poisoning in a case of rheumatic fever. Slocumb [99] reported the use by Frazer and Walsh [231] of intravenous injections of olive oil; reduction of fever and "adsorption of toxins by the minute fat globules" were presumably obtained. (Laboratory studies had not yet been carried out. The work has not been fully reported.—Ed.) With similar intent St. Jacques [232] gave colloidal charcoal intravenously. (The data are very meager. No conclusions can be drawn.—Ed.) When the hemoglobin fell below 50 per cent, Lyon [174, 175] gave periodic transfusions of 100 to 200 c.c. of blood.

Extra vitamin C was given by Rinehart [223] who was encouraged by preliminary results. However, no specific effect from vitamin C (530 c.c. of orange juice, or 200 to 300 mg. in crystalline form) daily for four weeks was noted by Faulkner.[225] The use of vitamins A and D "radiostoleum" appeared of little value to others.[168]

Tonsillectomy. Opinions on the value of tonsillectomy still differ. The majority favor early tonsillectomy if the tonsils are definitely diseased, but believe it should be done only when the disease is relatively inactive [159, 160, 167, 169, 203, 227, 229, 233] otherwise, an exacerbation may be precipitated. If the disease's activity is unusually persistent, tonsillectomy may have to be done while activity is present. (According to Robey, 1932, tonsillectomy even during activity of the disease can generally be done with safety and may be necessary if such activity is prolonged.—Ed.) As a prophylactic Lyon [175] advised salicylate therapy for 10 days before and after tonsillectomy. Some favor tonsillectomy on suspicion in all cases, even when tonsils are not obviously infected. Tonsillectomy does not prevent rheumatic fever, which may result from pharyngitis in a tonsillectomized child, but a clean throat will diminish a predisposition to upper respiratory infections. According to the large statistics of Kaiser,[29] the child who has had his tonsils out is less likely to have rheumatic manifestations, and if he does have them serious cardiac complications are less likely to develop. Although the incidence of recurrent attacks was not influenced by tonsillectomy, the mortality among 600 children was about twice as high in those who had tonsils at the time of the initial attack as in those whose tonsils had been removed. Gilkey [169] likewise found a 50 per cent lower mortality rate among those whose tonsils were out before the first attack. Preston,[166] however, found only a slight advantage for the tonsillectomized child.

Vaccines, Antitoxin. Attempts at desensitization by streptococcal vac-

cines and filtrates seemed worth-while to some,[169, 203] useless to others.[176] Streptococcal antitoxin (scarlatina) was used by Eason [228] in 37 cases; in 73 per cent "complete recovery" ensued after the use of 30 c.c. twice, 36 hours apart. Further doses had to be given to 27 per cent of the patients. Improvement began within 24 hours of the two initial doses. A brief febrile reaction usually preceded improvement. Serum rash and fever for one to two days later appeared in 32 cases. One patient died probably from a serum effect. Two of three control patients treated with normal horse serum also recovered. Because a few of the patients were relieved without developing febrile reactions, Eason believed that results were not entirely due to a foreign protein effect. No conclusions on the prevention of carditis were given.

(The use of three controls was insufficient. Foreign protein reactions may not need to be febrile to be effective. To date we would conclude that this "antitoxin method" gave nonspecific results, due to a foreign protein reaction.—Ed.)

Using scarlatinal toxin Coburn and Pauli [178] attempted active immunization of 113 normal persons. Skin reactions to streptococcal toxin were markedly diminished thereby, but there was no evidence that this treatment increased resistance to streptococcal infections or prevented rheumatic fever. Ten patients with quiescent rheumatic disease were given "passive immunization" with antitoxin (antistreptococcal serum). The introduction of these protective antibodies just prior to an expected attack (just after a streptococcal infection) did not decrease, and possibly increased, the intensity of the rheumatic recrudescence.

Fever Therapy with Typhoid Vaccine or Radiant Energy. Typhoid vaccine intravenously should be tried when salicylates fail, according to Cecil [234]; acute febrile polyarthritis may be thereby aborted. Although reactions to such vaccine, given when the disease is relatively inactive, may provoke a mild exacerbation, the disease thereafter may become more rapidly quiescent, according to Bland and Jones.[179]

Fever therapy was given by Sutton and Dodge [235] to 18 patients with active carditis. In 16 (who also had chorea) fever was produced by typhoid vaccine reactions, in two by radiant energy. From four to 14 fever sessions were given over a period of five to 26 days. In all cases clinical signs of activity of carditis completely subsided within 10 to 14 days after treatment. However, in some cases, relapses occurred after several months. The conclusions were that such fever therapy did not harm patients with subacute or inactive rheumatic carditis; it seemed to benefit them and deserved further study.

(The period of observation, about two years, was too short to permit final conclusions on the permanency of the effect. Further study is also required to confirm the apparently good immediate effects.—Ed.)

Splenectomy did not favorably modify the course of the disease.[178]

For Joints. Rest and salicylates continue as standard therapy. Splints properly applied are far superior to salicylates (Apfel [227]).

For the Heart. There are three objectives: (1) immediate relief of symptoms, (2) restitution of cardiac reserve to the greatest degree possible, and (3) maintenance of cardiac efficiency after the patient is up and about by a carefully planned and individualized regimen. Indications for digitalis, quinidine, and salyrgan or other diuretics have again been given.[174, 175, 200-202] The minutiae of a "cardiac regimen" are clearly set forth in several short readable papers which particularized the time for renewal of activity of the convalescent patient, the plan of graded activity and the method for recognizing the changing functional status of the heart.[176, 200, 202, 236] The physiologic effect of light muscle training was carefully studied by Proger and Korth.[237] The establishment of convalescent "hospital-schools" and cardiac camps has made much more effective the care of convalescent children.[176, 238]

To lessen cardiac strain and to prevent disaster in cases in which patients become pregnant, cesarean section under local or spinal anesthesia,[201] or induction of premature labor,[160] may be indicated.

For pericardial effusions Antell [184] preferred the use of oxygen tents for two to four days rather than paracentesis.

Prophylaxis. The prevention of the initial attack as well as of exacerbations depends at present on the fullest maintenance of a "physiologic life." [159] This necessitates the education of civic authorities to the value of smokeless, sunny cities with no overcrowding and with well-built homes, and the education of parents in "the wise nurture of children" with high resistance to disease—the prescription for which is good food, a proper ratio of rest and exercise, sunshine, frequent baths with contrast douches, the use of porous, light warm clothing, the removal of infected foci, and above all, the avoidance of respiratory infections by shunning crowds in unseasonable weather, and perhaps by the use of vaccines for children with repeated colds.[167, 203, 239] Particularly desirable for children are long stays in semitropical or tropical climates.

Sydenham's Chorea

Chorea may occur alone or with other manifestations of rheumatic fever, chiefly arthritis and endocarditis. Some consider it a disease in itself; others regard it as a symptom of rheumatic fever.[240, 241] Still others believe it may be a symptom of several diseases.[242] The close relationship of chorea and rheumatic fever is often very apparent. Considering chorea a single manifestation of rheumatic fever, Jones and Bland (Boston) [241] found that of 1000 cases of rheumatic fever, nearly 50 per cent (482) had frank chorea, the rest had other symptoms of rheumatic fever without chorea. Of the 482 that had chorea, 28 per cent had chorea alone; 72 per cent also had other symptoms of rheumatic fever. In the South chorea is rare. Of 224 pa-

tients with rheumatic carditis in Dallas, Texas, only four had chorea.[158] Chorea is considered a "white man's disease," rare in American Indians and negroes [243] and in the tropics. However, Kutumbiah [163] and Wig [162] noted several typical cases in India.

If chorea is a separate disease from rheumatic fever, according to Schwartz and Leader [240] one should expect the end of choreiform motions to signify the end of the disease; but if it is part of rheumatic fever, one may expect proof in the form of associated or subsequent carditis. Because in practically all of their 75 cases of "pure chorea" (no history and no evidence of rheumatic fever) carditis (myocarditis and mitral valvulitis) eventually developed within seven to eight years, Schwartz and Leader concluded that chorea is a symptom of rheumatic fever and that here also "the heart is always involved." In most cases the carditis developed insidiously, often without other attacks of chorea. In no case did aortic valvulitis, pericarditis or subcutaneous nodules develop.

These findings are in sharp disagreement with those of Jones and Bland.[241] Carditis developed in only 3 per cent of 134 cases of "pure chorea," those without other symptoms of rheumatic fever; the mortality was 0.7 per cent. In contrast, carditis developed in 86 per cent of 518 cases of rheumatic fever without chorea; the mortality was 32 per cent. It developed in 80 per cent of 184 cases of chorea which preceded other evidences of rheumatic fever, and in 60 per cent of 164 cases of chorea which followed other symptoms of rheumatic fever. The presence or number of attacks of chorea apparently did not influence the development of carditis. Thus Jones and Bland regarded "pure chorea" as a mild manifestation of rheumatic fever, one of good prognostic import but one in itself not especially conducive to carditis.

From a study of 150 cases Gerstley, Wile, Falstein and Gayle [242] concluded that chorea is not a disease but a symptom, more frequently of psychic trauma than of rheumatism. In their cases little relation to previous infection was found and no clinical evidence (no fever, leukocytosis, or increased sedimentation rate) of acute infection. Only 12 patients showed persistent signs of carditis. That other insults than rheumatism can cause chorea is also the suggestion of Hewins [244] who noted a case with neurosyphilis, of Lewis and Minski [245] who noted four cases with psychoses, and of Brian and Gerundo [246] who noted a fatal case of chorea gravidarum and concluded that, in pregnancy, one may encounter the Sydenham (rheumatic) variety or another type, a symptom of toxemia of pregnancy.

Treatment. Usual recommendations are rest and quiet, good nursing, sedatives, salicylates, pyramidon, arsenic or stramonium, but, unaffected thereby, the disease may run its usual course of six to 10 weeks or longer.[233, 243, 247] Jones [247] found streptococcal vaccine valueless. Small's antiserum (1927) helped only 13 per cent of Wetchler's [243] patients.

Tonsillectomy. Jones [247] considered tonsillectomy indicated in cases of

chorea with other rheumatic symptoms, but not particularly in "pure chorea." It should be done only when the disease is quiescent. Tonsillectomy has no effect on the course, duration or tendency to recurrences of chorea, but the tonsillectomized patient with chorea is much less likely to have endocarditis.[242]

Nirvanol. Results from nirvanol were satisfactory to Wetchler,[243] who had no complete failures in 115 cases. The disease was generally terminated within three weeks, although recurrences were not prevented. The plan of treatment and the "nirvanol reaction" were described and a brief review of the literature was given. Twenty-one moderately severe and five severe cases were treated by Bender and Pratt [248] with good results. Two patients had recurrences within a year. No harmful effects and no fatalities were encountered. Jones [247] used nirvanol in three cases; one patient had no febrile reaction and obtained no relief; another was unrelieved and a "very serious, almost fatal reaction with suppression of bone marrow" developed. Jones considered it a dangerous drug and its use unjustified.

Fever Therapy. Some believe that the results with nirvanol and other fever-producing substances are due to the fever. Jones [247] used typhoid vaccine for fever therapy; his results (not fully reported) were not striking. The results of Sutton and Dodge (1933) with typhoid-vaccine fever reactions, however, were very striking; attacks were thereby shortened by an average of 36 days as compared with results when physical therapy, drugs, and diets were used. The average duration of attacks of 150 patients treated by vaccine reactions was 8.5 days, that of 150 patients treated otherwise 42.6 days. Sutton and Dodge [235, 249] recently noted similarly good results with "artificial fever." Foreign protein shock is avoided, fever is controllable, and only one or two sessions (105° to 106° F. for five hours) instead of several daily reactions are necessary. Associated active carditis was not aggravated, indeed seemed to be benefited thereby.

Desjardins and Popp [45, 72] considered artificial fever therapy most effective. All of nine children "improved satisfactorily." Daily fever sessions, at 103° to 104° F. for three to four hours, were given for one week. "In a week's time the attacks had passed." Two patients with chronic chorea treated by Hefke [45, 51] were "improved," and of seven previously treated unsuccessfully with typhoid vaccine, six were controlled by artificial fever given by Schmidt.[45] Nine of 12 children treated by Schnable and Fetter [52] were "cured" after an average of four fever sessions and had no recurrences within several months. Two children treated with low temperatures were only partially relieved. One child died 17 hours after collapsing during the first partial fever session as a result of a disturbance of the heat-regulating mechanism. In spite of this they regard fever therapy as offering the best chance of cure. (For comments on the general safety of fever therapy, the avoidance of unfavorable reactions and the probable inevitability of an occasional fatal reaction, the reader is referred to the discussion on fever therapy under "Treatment of gonorrheal arthritis."—Ed.)

Chronic Arthritis

Incidence. More statistics on the incidence and types of arthritis seen in general practice are needed. More available are statistics on the relative incidence of different types of arthritis seen in special clinics. Of 400 consecutive patients with "chronic arthritis" at the arthritis clinic of the Presbyterian Hospital, New York, 75 per cent had atrophic or hypertrophic arthritis.[34] Of 200 consecutive patients with acute or chronic "rheumatic diseases" seen at The Mayo Clinic, 65 had atrophic arthritis, 39 hypertrophic arthritis; 30 had both types and 66 had other types of arthritis.[106] Of Lang's [250] 100 patients with chronic arthritis 47 per cent had atrophic, 21 per cent hypertrophic arthritis; 28 per cent had both types (and 4 per cent other types of arthritis?—Ed.) Of Gray's [251] patients with chronic arthritis 70 per cent had atrophic, 30 per cent hypertrophic arthritis.

General Remarks on Etiology and Relationship of the Two Great Types. There are four different opinions on the relationship between atrophic and hypertrophic arthritis: (1) that they are quite separate diseases of different etiology, the opinion of the majority [34, 252]; (2) that the two types should be regarded as separate clinical entities, but may well have a common (but variable) etiology [253]; (3) that the two types are variants of one disease, caused by any one of a number of agents, and (4) that the two types are manifestations of one disease and have a single etiology. Thus both types were ascribed to "cold edema" by Biorkman,[254] to a sulphur deficiency, particularly of cartilages by Wheeldon.[255]

Distinctions Between the Two Great Types. Clinical distinctions remain as previously reported.[1, 2] Pathologic distinctions between the two types were again described by Parker and Keefer [256] who insisted that the gross and histologic features of each are quite different even when both coexist in the same case. They therefore regarded as untenable the idea that both may result from the same underlying factors.

Roentgenographic alterations which appear as each type progresses were again reviewed by Doub [11] and by Ferguson, Kasabach and Taylor,[29] who analyzed 49 roentgenographic characteristics. Since varieties of bone atrophy, lipping and zones of erosion are common to the roentgenograms of many different types of arthritis (atrophic, hypertrophic, gouty, gonorrheal, tuberculous and others), it is agreed that there is no one pathognomonic feature in any one type. Each, however, has its characteristic picture or combination of alterations which may make the roentgenogram in a given case highly suggestive. These alterations, best seen in roentgenograms of hands, feet and knees, are as previously reported.[1, 2]

(Roentgenographic features of each type have been described in numerous reports. Studies now much more to be desired are those on serial roentgenograms of the different arthritides—consecutive pictures taken of the same patients from the onset to the inactive stage of the disease. Such data, now very meager, are needed to determine the natural course of the disease and to establish the average and the minimal and maximal time that elapses between the disease's onset and the appearance

of each of the various roentgenographic abnormalities. Among the practical questions thus answered would be: How long must a roentgenogram of a painful joint remain "negative" before one can conclude that the disease in a given case is periarticular, not intra-articular, and probably represents periarticular fibrositis and not a mild slowly progressive atrophic arthritis?—Ed.)

Chemical differences between the two types of arthritis have been noted by several [29, 34, 257–260] and are as follows: In atrophic arthritis the sedimentation rate is usually more than 30 mm. in one hour: agglutinins to hemolytic streptococci are usually present in high titer. There is an increase in plasma fibrinogen and globulin fraction, a fall in the albumin fraction, and the albumin-globulin ratio is frequently less than 1. Serum calcium is essentially normal and the plasma cholesterol tends to be decreased. In hypertrophic arthritis the sedimentation rate is rarely more than 20 to 30 mm.; agglutinins to hemolytic streptococci and abnormal values for plasma fibrinogen, albumin and globulin are generally absent, the serum calcium is normal or slightly subnormal, and the plasma cholesterol tends to be elevated. These chemical differences lend support to the theory that the two types of arthritis are quite different diseases.

Constitutional differences have long been suspected, it being frequently stated that atrophic arthritis tends to appear in tall, thin, visceroptotic persons; hypertrophic arthritis in short, stocky, obese, sthenic individuals. According to Pribram [261] who determined the biotype of the two, the brachymorphic group rarely develops atrophic arthritis but has a decided tendency to develop hypertrophic arthritis. Thus of 24 patients with atrophic arthritis, 15 were eumorphic (normal body build), 9 dolichomorphic (tall, thin, shallow-chested, underweight); none was brachymorphic (short, thick overweight). Of 26 patients with hypertrophic arthritis, 8 were eumorphic, 16 were brachymorphic and 2 dolichomorphic. However, there are frequent exceptions to these generalizations. Dawson [103] frequently noted atrophic arthritis in the short, obese, pyknic type and hypertrophic arthritis in the tall thin type (though perhaps not quite as early as in the former).

Atrophic Arthritis

Incidence. Atrophic arthritis is presumably much less common in the tropics than in temperate zones. However, new reports indicate that it is fairly common in Egypt (Abdel-Sayed).[262] In Australia it is more common in the southern (temperate) regions (Cooper [161]) than in the northern (tropical) states; in the latter it is less common than rheumatic fever.

Symptoms and Course. Howitt [263] stressed the importance of recognizing the "rheumatic diathesis," and the prodromes of atrophic arthritis: loss of appetite and weight, tachycardia, a fall in blood pressure, slight fever, sweating hands and feet, tremors, general nervousness, extreme fatigability —"symptoms referable to overstimulation of the katabolic group of endocrine glands." Although atrophic arthritis may begin at any time of the year, its greatest seasonal incidence in Dawson's [103] cases in New York City

was in the spring, especially March. In more than 80 per cent of his cases the onset was between the ages of 20 and 50 years, the greatest incidence being at 35; the earliest onset at 14 months and the latest, at 78 years. Three females were affected to one male. Although the onset of the disease is usually insidious, and occasionally subacute, it was acute in 8 per cent of his cases, at first resembling rheumatic fever. In 100 consecutive typical cases mitral stenosis was found in 7 per cent.

Subcutaneous nodules are present in about 20 per cent of cases.[103] According to Neligan [264] there are two types of nodules in atrophic arthritis: "millet seed nodules," described by Coates and present also in "rheumatic children without cardiac lesions," and larger nodules, often painful, which may be an inch or more in diameter and may persist for years. Neligan saw a 59 year old woman with atrophic arthritis who had over 100 nodules in different sites, varying in size "from an inch across to that of half a split-pea." They were intermittently painful; pressure sores had formed over some.

Atrophic Arthritis and Splenomegaly; Relation to Still's Disease and to "Felty's Syndrome." Adenopathy is common in atrophic arthritis, occurring in from 40 (Douthwaite, 1933) to 53 per cent of cases (Coates and Delicati, 1931). An enlarged or palpable spleen is present in from 10 to 15 per cent (Dawson [103]) to 21 per cent of cases (Coates and Delicati). Atrophic arthritis, adenopathy, and splenomegaly in adults have been called by some "adult Still's disease," but the majority regard Still's disease of children or of adults as a variety of atrophic arthritis. Moncrieff [104] did not accept this view and regarded Still's disease and juvenile atrophic arthritis as different diseases. He considered unproved the idea of certain continental physicians that Still's disease is of tuberculous origin.

Chauffard (1896) and Still (1897) described the syndrome of arthritis, adenopathy and splenomegaly. Hepatomegaly was not mentioned by either; anemia was emphasized by Chauffard but not by Still. In Still's cases joints were enlarged but no changes in bone or cartilage occurred even in advanced cases, hence the distinction from juvenile or adult atrophic arthritis. In 1909 Herringham noted the association of arthritis, splenomegaly and hepatomegaly in adults. In 1924 Felty reported cases of chronic arthritis, splenomegaly, anemia and leukopenia, and debated whether they were cases of adult Still's disease, arthritis coincident with Banti's disease, or of a distinct clinical entity.

Fitz [265] continued the discussion on relationships and described a case of "Still's disease" and one of "Felty's syndrome." In the former case deforming arthritis and splenomegaly were present but no adenopathy. No description of roentgenograms was given to indicate whether or not intra-articular disease was absent, as described by Still. The patient with "Felty's syndrome" presented deforming arthritis, hepatomegaly, splenomegaly, anemia and leukopenia, and died suddenly of an undetermined cause.

Castellani [266, 267] distinguished between "Still's disease" and "febrile hepato-splenomegaly of adults with arthritis," describing 3 cases of the latter, of men aged 45, 54 and 61 years. Features of the disease were slow onset of malaise, arthritic pains, a somewhat undulating irregularly-intermittent or remittent fever, and great enlargement and firmness of the liver and spleen. One or several large or small joints were swollen and painful. Adenopathy was absent. The blood picture varied: slight leukocytosis, slight leukopenia or a normal blood count were present at different times in the same cases. Various agglutinins were absent. The disease was progressive. In one case death occurred in 14 months. Because "in Still's disease there is no true hepato-splenomegaly, the spleen being palpable but not much enlarged, and the liver usually of normal size" Castellani did not regard his cases as being ones of Still's disease.

(Obviously various physicians define Still's disease differently. As we stated before [2] it is interesting to note variations in the response of the reticulo-endothelial system in cases of arthritis, but a new name for each combination seems unjustified. Dawson [103] thought there was no merit in the clinical segregation of "Felty's syndrome" or in the use of the term itself, which should be discarded. Until other evidence is available, we favor considering these "syndromes" as varieties of atrophic arthritis.—Ed.)

Pathology. Pathologic changes in three cases of atrophic arthritis were described by Parker and Keefer.[256] Primary changes were synovitis, characterized by an increase in the number of synovial cells, with thickening of the membrane, destruction of some synovial cells, and collections of lymphocytes, macrophages, plasma and rare giant cells. In some regions these collections were perivascular (as described by Fisher, 1929); in others they were not perivascular (as described by Allison and Ghormley, 1931). In the fat of periarticular tissue were perivascular lymphocytic infiltrations; in periarticular muscle there was degeneration and atrophy. Secondary changes were: destruction of cartilage, atrophy of bone due to disuse and not to active destruction, subluxation, fibrous or bony ankylosis and muscular atrophy. Additional changes were lymphoid hyperplasia, calcification of blood vessels, amyloidosis, disturbances of growth and pigmentation of skin. Parker and Keefer do not agree with Nichols and Richardson (1909) or Allison and Ghormley on the mechanism of cartilage destruction. The latter stated that as the synovial pannus passes over cartilage, it adheres and destroys the cartilage, which is simultaneously being invaded and destroyed by connective tissue proliferation from subchondral spaces. Parker and Keefer believed that cartilage destruction is not necessarily from subchondral invasion, but from a solution of cartilage under the connective tissue pannus and from a "dedifferentiation" of cartilage into connective tissue.

(Much can be learned from pathologic specimens, from whatever source obtained. However, it is unfortunate that clinical histories in two of Parker and Keefer's three cases were not available. The errors and inadequacies of Nichols and Richardson's

otherwise admirable report resulted from a paucity of clinical data. Pathologic reports of cases fully studied from the clinical, chemical and roentgenologic standpoint are highly desirable.—Ed.)

Laboratory Data: Blood Counts and Hemoglobin. Anemia is commonly present in atrophic arthritis, but it is evidenced by a reduction in hemoglobin content rather than in erythrocyte count. In 92 cases Collins [268] noted only a minor reduction of erythrocytes, but the value for hemoglobin was normal (14 gm. or more) in only 18 per cent. The value for hemoglobin was 13 to 14 gm. in 26 per cent, 12 to 13 gm. in 30 per cent, 11 to 12 gm. in 13 per cent, 10 to 11 gm. in 11 per cent and less than 10 gm. in 2 per cent. This simple hypochromic anemia was much more frequent in females and bore no constant relationship to gastric anacidity. Severe anemia was seen in patients with normal gastric acidity. Gray, Bernhard and Gowen [269] found anemia much oftener among clinic than private patients owing to the poorer living conditions and more advanced arthritis of the former. Hemoglobin was less than 80 per cent in 50 per cent of their private patients and in 81 per cent of their clinic patients. Erythrocytes were below four million in 14 per cent of private patients, in 39 per cent of clinic patients. As the disease progressed the value for hemoglobin dropped. In early cases a leukocytosis (over 10,000) and a shift to the left were more frequent. Steinberg [270] found the Schilling hemogram shifted to the left in 78 per cent of 42 cases of atrophic arthritis, but in only 17 per cent of 17 cases of hypertrophic arthritis. Correlated abnormalities in both blood counts and sedimentation rates were generally found, but when disagreement was noted, Steinberg considered an abnormal Schilling count of more value than the sedimentation rate in differentiating the two types of arthritis.

Sedimentation Rates. The value of this test in the differentiation and prognosis is reaffirmed by several.[29, 34, 196, 251, 269] Gray [251] noted the following: In early atrophic arthritis, rates were 0 to 10 mm. (per hour) in 23 per cent; 10 to 20 mm. in 37 per cent; more than 20 mm. in 40 per cent. In "established arthritis" they were 0 to 10 mm. in 14 per cent; 10 to 20 mm. in 25 per cent; more than 20 mm. in 61 per cent. In "advanced arthritis" they were 0 to 10 mm. in 8 per cent; 10 to 20 mm. in 25 per cent; more than 20 mm. in 87 per cent. Rates were more than 20 mm. in only 2 per cent of cases of hypertrophic arthritis. The rate of sedimentation is believed to depend largely on the concentration of plasma fibrinogen and globulin and on cell volume.

Blood Proteins. To determine reasons for altered sedimentation rates Davis [29] studied blood proteins. The total proteins of blood were normal in both atrophic and hypertrophic arthritis but, in atrophic arthritis, there was an increase in plasma fibrinogen and globulin, particularly the euglobulin fraction, and a fall in the albumin fraction. The albumin-globulin ratio was frequently below one, but tended to become normal as the patient recovered. Since rises in plasma globulin often occur in infectious diseases, Davis con-

sidered this evidence that atrophic arthritis is an infection. These alterations in proteins were not seen by Davis in hypertrophic arthritis. The findings of Aldred-Brown and Munro [257] were essentially similar except that they found in hypertrophic arthritis also a reduction of serum albumin, though not nearly so much as in atrophic arthritis.

Cholesterol. The total plasma cholesterol tends to be decreased in atrophic arthritis (increased in hypertrophic arthritis, Hartung and Bruger [259]). The mean total cholesterol in 33 cases was 175.2 ± 39.5 mg. per 100 c.c. of plasma. The cholesterol was normal (160 to 230 mg.) in 49 per cent, below normal in 39 per cent and above normal in 12 per cent. The cholesterol partition (free: ester) was normal. No correlation existed between sedimentation rates and cholesterol. Hypocholesteremia tends to support the infectious theory since other acute infections are accompanied by it.

Serum Calcium and Phosphorus. Normal values were found in the 200 cases of Lahey and Haggart [271] and in all but one seen by Gray, Bernhard and Gowen [269]; one case had a low calcium-phosphorus index. Hartung and Greene [258] found the values for the mean and standard deviation in 50 cases to be 10.218 ± 0.699 mg. calcium per 100 c.c., the same as in control cases. The serum calcium was slightly lower in hypertrophic arthritis. These findings do not quite agree with those of Race [260] who noted a small but definite tendency to lower values in atrophic than in hypertrophic arthritis.

Magnesium. Serum magnesium was essentially normal in both types of arthritis (Race [260]). Values were slightly lower in atrophic than in hypertrophic arthritis.

Blood Groups. In 1000 cases of rheumatism (atrophic and hypertrophic arthritis, "subacute rheumatism," fibrositis) Race [260] found the blood groups that would be expected from a random sampling of the general population.

Blood Pigments. In cases of atrophic arthritis with a rapid sedimentation rate Race [260] often found a marked diminution of plasma pigments. The icteric index was often as low as 3 units, sometimes even lower (normal about 6 units). Studies were in progress to determine whether the low plasma color was due to reduced lipochromes, bilirubin or both.

(These observations are of interest in connection with those of Hench (1933-34)[49] and of Sidel and Abrams (1934) that jaundice may induce a rapid and prolonged remission in cases of atrophic arthritis and of fibrositis.—Ed.)

Urine. Ellis (1927) and others suggested that there was an "alkaline diathesis" (deficient acid elimination) in atrophic arthritis, an "acid diathesis" (deficient alkali elimination) in hypertrophic arthritis. Race [260] was unable to substantiate this contention. Urinary calcium was normal, and the pH, acidity, formol acidity and phosphate excretion were equal in both types.

Gastric Analysis. Among 53 patients with atrophic arthritis Collins [268] noted achlorhydria in 23, hypochlorhydria in five, normal acidity in 23 and

hyperchlorhydria in two. Reduction of acids bore no constant relation to anemia present. Hartung and Steinbrocker [272] noted achlorhydria in 27 per cent, hypochlorhydria in 17 per cent of 35 cases of atrophic arthritis; and achlorhydria in 26 per cent, hypochlorhydria in 3 per cent of 35 cases of hypertrophic arthritis. They considered that an abnormal frequency in the occurrence of subacidity is an important feature of chronic arthritis.

Electrocardiograms. The electrocardiograms in 50 cases of acute atrophic arthritis were found to be essentially normal by Master and Jaffe,[193] in sharp contrast to those in cases of acute rheumatic fever.

Synovial Fluid. Normal synovial fluid probably contains about 200 cells per cu. mm. of which less than 10 per cent are polymorphonuclear cells, according to Collins.[273] The total nucleated cell counts in 35 cases of atrophic arthritis were high (5,000 to 60,000 cells per cu. mm.). Counts in most cases were 10,000 to 20,000 cells. The percentage of polymorphonuclear cells varied from 40 to 90 per cent, in the great majority of cases being 70 to 90 per cent. These data agree essentially with those of Keefer, Myers and Holmes (1934). The consistently elevated protein content of synovial fluid indicated the presence of an exudate, not a transudate. The ratio between blood and synovial sugar content was never significantly altered in atrophic arthritis. (In bacterially-infected fluids in specific infectious arthritis synovial sugar is usually markedly reduced.—Ed.)

Etiology and Pathogenesis. The literature of 1935 repeated familiar arguments on etiology. Factors previously considered are again regarded as causal: the factor of infection, of trauma, of circulatory disturbance, of altered metabolism, of endocrine abnormality, and of neurogenic disturbances. Each factor is regarded by some as the essential one, the other factors being contributory.

Factor of Infection. Evidence for the theory of infection is direct and indirect. Direct evidence is presumably derived from cultures of blood, infected foci, lymph nodes, joint tissues and fluid, and from studies on the tropism and cataphoretic velocity of bacteria isolated therefrom.

1. *Blood cultures.* Gray [251, 269] and his colleagues reported isolation of streptococci, mostly alpha (viridans) or alpha prime, from the blood in 48 per cent of 200 cases. Cases of early arthritis gave a much higher (65) percentage of positive cultures than those of established arthritis (positive in 36 per cent) or of advanced arthritis (positive in 26 per cent). Few positive blood cultures were obtained in summer. Cultures from infected foci often yielded the same types of streptococci. A small percentage of blood cultures yielded staphylococci and diphtheroids of undetermined significance. Control blood cultures were negative in all of 36 "normal" persons, and in all of 79 cases of hypertrophic arthritis; they were positive in 23 per cent of 22 cases of "acute focal infection," in 4 per cent of 26 cases of "chronic focal infection," and in 8 per cent of 89 cases of "arthralgia." (Were the latter cases of periarticular fibrositis?—Ed.)

Streptococci, generally "viridans," occasionally "hemolytic," were found

in 21 per cent of patients with atrophic arthritis, in 6 per cent of controls, by McEwen, Bunim and Alexander.[29]

2. *Other cultures.* Although a variety of methods was used, cultures of synovial fluid were all negative in Collins' cases.[273] Key [29] was unable to isolate streptococci from articular tissues, but found staphylococci in a third of joints studied. Streptococci of the alpha (viridans) or gamma (nonhemolytic) type were found by Gray and his colleagues [251, 269] in 30 per cent of stools examined.

3. *Electrophoretic velocity.* Rosenow [274] again noted that streptococci, isolated in cases of atrophic arthritis and having a marked affinity for joints of animals following intracerebral injection, had a markedly "arthrotropic" cataphoretic velocity, usually 2.3 microns per second, volts per centimeter. Streptococci similarly isolated in cases of encephalitis had little or no affinity for joints but marked affinity for brains of animals and a markedly "neurotropic" cataphoretic velocity, usually 3.45 or 1.72 microns per second, volts per centimeter. The velocity of streptococci isolated from patients with "neuromyositis" was distributed between neurotropic and arthrotropic, about half of them having a neurotropic, the other half an arthrotropic potential. Previous similar work by Rosenow and Jensen (1930) was confirmed by Wood, Jensen and Post [275] who studied the cataphoretic velocity of streptococci (generally viridans, occasionally hemolytic, rarely the "indifferent" type) isolated from 1173 cultures from foci in 215 cases of "focal infection diseases" including 90 cases of atrophic arthritis and 70 of neuritis. The method of cataphoresis was found useful in detecting reactions between antibodies and homologous bacteria. Given a stock suspension of bacteria with known pathogenicity and known mobility, specific antibodies in a patient's serum could be detected.

When Pratt, Sheard and Rosenow exposed them to short-wave radiation, arthrotropic streptococci lost their characteristic arthrotropic electrical potential and their affinity for joint tissues, and assumed the velocity of neurotropic bacteria and an affinity for brain. Conversely, neurotropic streptococci became arthrotropic and acquired affinity for joints. Changes thus induced were maintained in subcultures of these organisms.[276, 277]

(These experiments were done on bacteria in vitro. Do they suggest that exposure of an arthritic patient with arthrotropic streptococci to short wave therapy might change the invasive character of the patient's bacteria and his symptoms and make him "neuritic"? Rosenow's clinical colleagues treated a few arthritic patients with short wave therapy. Such clinical mutations, perhaps theoretically possible, have not been noted by them, or reported by others using short wave therapy.—Ed.)

4. *Indirect evidence.* Indirect evidence supporting the infectious theory is derived from skin reactions to injections of certain bacteria, from the presence of agglutinins, precipitins, antifibrinolysins, and antistreptolysins, and from complement-fixation reactions.

a. Skin tests. "Positive skin reactions" to one or more strains of

streptococci were found by Wainwright [278] in 75 of 78 cases. A maximal reaction was to hemolytic streptococci in 88 per cent, to green streptococci in 8 per cent. Three cases showed no reactions. Skin reactions were absent in two and present in one case of Still's disease, absent in four and present in six cases of hypertrophic arthritis. Reactions diminished or disappeared when patients were treated with vaccines made from streptococci to which their skin was sensitive. Keefer [279] and Dawson [103] have reminded us of the wide divergence in results obtained with such tests, and that their interpretation is difficult. All arthritic patients do not show positive reactions; some may react to organisms not found in their foci. In a given case a " positive skin test " does not in any way prove a causal relationship between the bacteria used and the patient's disease, although it may suggest that the patient is either infected with or is a carrier of the bacteria in question.

b. Agglutinins. Agglutinins to hemolytic streptococci, generally in high titer, were found in serums by Wainwright [278] in 90 per cent of 87 cases; by McEwen, Bunim and Alexander [29] in 88 per cent of 37 cases; by Blair and Hallman [206] in 85 per cent of 62 cases. According to Dawson [103] significant agglutination occurs only with hemolytic streptococci, group A (Lancefield). Agglutinins for this group were usually definitely present in the cases of McEwen, Chasis, and Alexander,[280] but definite reactions were also obtained with other hemolytic streptococcal groups. Of Gray's [251] cases, 70 to 76 per cent had agglutinins (presumably to green streptococci, " alpha or alpha prime ") in dilutions from 160 to 5120. Blair and Hallman [206] found no correlation between agglutinin titers and the patient's age, duration of arthritis, number of joints involved or sedimentation rate. Others [269] found it difficult to understand why titers increased in some and decreased in others who were progressing satisfactorily, and why titers increased one month and decreased the next. During the treatment of Wainwright's patients with streptococcal vaccine the agglutinins materially increased.[278]

The presence of such agglutinins is regarded by many [103, 278, 279] as the strongest evidence in favor of the infectious theory of atrophic arthritis. They are found only rarely in patients with hypertrophic arthritis or in normal persons.[103, 206, 278] Because, however, hemolytic streptococci can be isolated so rarely from affected joints, and because antifibrinolysins are *not* increased in atrophic arthritis (as they are in proved hemolytic streptococcal diseases and in rheumatic fever), one cannot finally conclude that the presence of streptococcal agglutinins indicates a causal relationship (Wainwright [278]). Keefer [279] raised the question: Are these reactions a direct response to streptococcal infections, or are they indirect responses of a nonspecific nature such as one sees in syphilis and typhus fever?

Formerly, Rawls and Chapman [281] treated patients with vaccines made only from strains which patients' serums agglutinated, and inagglutinable strains were discarded as of no etiologic significance. Because some patients

so treated did not receive benefit, it was surmised that agglutination tests might not be reliable criteria for determining pathogenic specificity, since some causal strains might be inagglutinable. (Freshly isolated strains of typhoid bacilli are sometimes inagglutinable.—Ed.) Seeking more reliable tests of specificity, Rawls and Chapman [281] determined not only the agglutination tests, but the ability of strains of streptococci (isolated from infected foci of arthritic patients) to resist the " bactericidal " action of freshly-diluted defibrinated guinea-pig's blood in conjunction with their ability to produce arthritis in rabbits. Agglutinable strains killed by guinea-pig's blood produced arthritis in 88 per cent of injected rabbits, although large doses and multiple injections were required. Non-agglutinable strains killed by guinea-pig's blood produced arthritis in only 30 per cent of injected rabbits. Agglutinable strains not killed by guinea-pig's blood produced arthritis in 92 per cent of injected rabbits. The most pathogenic, however, were non-agglutinable strains not killed by guinea-pig's blood: these produced arthritis in 100 per cent of injected animals. Rawls and Chapman therefore concluded that certain inagglutinable strains were more pathogenic than agglutinable strains, particularly if they were also resistant to the bactericidal effect of guinea-pig's blood, and that agglutination tests in conjunction with tests of the resistance of a strain to the bactericidal action of guinea-pig's blood are of more value in assaying the specific pathogenic potentialities of any particular streptococcus than agglutination tests alone.

c. Precipitins. Precipitins for the C substance of hemolytic streptococci were found by McEwen and his colleagues [280] in the blood of 80 per cent of 37 patients with atrophic arthritis, but they were also frequently found in other types of arthritis, even gonorrheal. In appraising their significance, therefore, caution must be exercised. There is a close approximation but not an absolute agreement between agglutination and precipitin reactions (Dawson [103]).

d. Antistreptolysins. Antistreptolysins were increased (over 100 units per c.c.) in the blood of only a few of McEwen's [29] patients, and in the blood of only a third of Blair and Hallman's 45 patients.[206] In the latter cases high antistreptolysin titers with one exception accompanied high agglutinin titers. Of 32 miscellaneous serums tested for antistreptolysin, only seven gave high titers, two from cases of atrophic spondylitis, five from cases of chronic osteomyelitis.

e. Antifibrinolysins. Antifibrinolysins were not found by Myers, Keefer and Holmes [208] in plasma in 11 cases and were only occasionally found by McEwen.[29] Since antistreptolysins and antifibrinolysins are indexes of recent, acute, hemolytic streptococcal infection, perhaps one should not expect to find them in cases of chronic atrophic arthritis, although they are sometimes found in early acute cases.

f. Complement-fixation tests. These tests with streptococci were usually negative in cases of " acute or chronic polyarthritis " seen by Beck and

Coste.[207] They were usually positive to several streptococci, staphylococci and colon bacilli in the few cases of Gray et al.[269] who regarded the test subject to considerable error unless rigidly controlled. An occasional patient with atrophic arthritis gave an unexplained positive complement-fixation test to gonococci.

5. *Interpretation of evidence for the theory of infection.* Investigators are discouraged in their attempts to discover direct indisputable evidence for this theory, hence their activity in searching for strong indirect evidence from various serologic and other reactions noted. An interpretation of these reactions is not now possible. Most of them are only relatively specific for atrophic arthritis; they are generally not specific for one bacterial strain and at best suggest, but do not prove, a causal association with streptococci. Indirect or circumstantial evidence is never as satisfying or convincing as direct evidence; nevertheless one cannot disregard it. One cannot deny the value of indirect evidence if it is found to be practically "specific." In the diagnosis of syphilis we have learned to rely heavily on the indirect evidence of an accurate serologic reaction; we no longer hunt for direct evidence—the *Spirochaeta pallida.* This analogy is worthy of further comment: The value of a positive Wassermann reaction lies in the fact that it is only "specific" to the extent that it is essentially pathognomonic of syphilis for the actual presence of spirochetes is not necessary for the reaction. Some by-product of the disease is responsible for the reaction. Hence it is possible that various streptococcal immune bodies in atrophic arthritis (and rheumatic fever) are by-products of the disease, responsible for reactions which may be proved to be more or less "specific" or pathognomonic of atrophic arthritis even though streptococci may not actually be the specific cause of the disease. Evidence for the theory of infection continues to be highly suggestive but is not yet conclusive.

The Theory of Bacterial Allergy. Hypersensitiveness, not to one, but to several bacterial strains, proposed as a way out of this dilemma, is accepted by some,[282] but is meeting with increasing objections from others. Freeman's [220] criticism of the theory was noted under the discussion on rheumatic fever. Keefer [279] also regarded it as unproved. Although in many ways the hypothesis sounds attractive, Dawson [103] concluded that "it is supported by singularly little evidence."

Virus Theory. Coles [222] found "numerous virus bodies" in the synovial fluid in five of nine cases of atrophic arthritis. He regarded them of the same species as those he found in cases of rheumatic fever. No animal studies were made, hence no conclusions could be drawn.

Factor of Trauma. That acute or chronic trauma from occupation, poor posture or recreation can predispose to, precipitate or aggravate atrophic arthritis is again emphasized by Hall [13] and by Archer.[283] The latter believed that repeated trauma may produce atrophic as well as hypertrophic arthritis.

Factor of Circulatory Disturbance. No new definite evidence is presented. Biorkman [254] regarded the local and systemic manifestations of atrophic or hypertrophic arthritis (as well as of fibrositis) as caused by local exudation from "cold edema."

(No proof is offered.—Ed.)

Keefer [279] and Dawson [103] cannot accept the idea that atrophic arthritis is caused by circulatory disturbances, because arthritis is not a complication of occlusive vascular disease and is infrequently associated with Raynaud's disease or scleroderma, because delayed removal of sugar from the blood of arthritic patients is variably present and also present in certain non-arthritics, and particularly because synovial membrane in atrophic arthritis reveals, not a decreased, but rather an increased blood supply, with many wide open capillaries.

(These pathologic findings link up with the bone atrophy present, for Jones and Roberts, 1934, found that bone becomes partly decalcified when its blood supply is increased, but becomes hypercalcified if its blood supply is decreased.—Ed.)

Factor of Altered Metabolism. Current theories are that there is a disturbance of sulphur metabolism, of liver function, or a vitamin deficiency, a food allergy, or an intestinal toxicosis. The origin of the idea that arthritis may result from abnormal sulphur metabolism has been reviewed by several.[255, 284-287] The cystine content of certain tissues, such as finger nails, is considered a reliable guide to the sulphur metabolism of the body. The normal cystine content of nails ranges from 10.4 to 13 (average about 11.8) mg. per 100 c.c. (Wheeldon,[255] Rawls, Gruskin and Ressa,[284] Argy,[288] Sullivan and Hess, 1934). In "arthritic patients" the range is 6.5 to 13 mg. (average variously reported at 8.2 to 9.8) (Sullivan and Hess, 1934; Argy,[288] Woldenberg [285, 286]). The range in Woldenberg's patients was 6.5 to 9.8 mg. before, and 11.6 to 13 mg. after, sulphur therapy. The cystine content of nails and the sedimentation rate of erythrocytes varied in inverse proportion.[288] Hess [289] noted these concentrations in normal nails: cystine by the Sullivan method, 11.98 mg. per 100 c.c., and by the method of Vickey and Block, only 9.57 mg.; arginine 6.6 per cent, histidine 0.46 per cent, and lysine 2.61 per cent. In the nails of patients with "arthritis" Hess found: cystine, 9.78 per cent (Sullivan method); arginine, 6.62 per cent; histidine, 0.49 per cent; lysine, 2.63 per cent. Thus in nails of arthritics the three basic amino-acids were essentially normal, but the cystine was reduced. These workers made no attempt to subdivide "chronic arthritis." In atrophic arthritis Wheeldon [255] found the cystine content of nails was 7.9 to 10.6 (average 9.65) mg.; after sulphur therapy the average rise was 1.63 mg. (In hypertrophic arthritis the content was 8.2 to 10.6, average 9.27 mg.; after sulphur therapy the average rise was 2.35 mg.)

Because of these findings Wheeldon [255] suggested that "at least some, if not all, forms of arthritis are made possible by a sulphur deficiency, par-

ticularly in the cartilage of the joints; that, given a sufficient sulphur reserve to combat the contributing etiologic factor, arthritis would not occur; and that, whether there is a sufficient sulphur reserve or not depends upon the ability of the intestinal tract normally to absorb sulphur."

Race [260] does not interpret the findings thus. The lowered cystine content of nails may be due, not to a disturbance of general sulphur metabolism, but to the reduced albumin-globulin ratio in blood plasma. The cystine content of globulin is lower than that of albumin, and the amount in nails may merely reflect alterations in plasma proteins. In a few cases of atrophic arthritis Race found a reduced blood glutathione, which probably resulted from the reduced number of erythrocytes as there is little or no glutathione in plasma. (Other evidence has been presented in favor of an abnormal sulphur metabolism. Goldthwaite (1904) noted loss of sulphur in atrophic, and sulphur retention in hypertrophic arthritis. Cawadias (1925) reported a negative sulphur balance, indicating increased sulphur catabolism in "chronic rheumatics." Race (1927) denied the existence of a negative balance but noted increased urinary excretions of neutral sulphur in 20 of 42 patients with atrophic arthritis.—Ed.) Senturia [287] studied the sulphur excretion and partition in the daily urine of 18 patients with atrophic and 41 with hypertrophic arthritis. No appreciable deviations from those in 20 healthy persons were noted. His experiments tend to disprove the alleged existence of abnormal sulphur elimination or sulphur partition in the urine of arthritics.

Hepatic Dysfunction. This is regarded by Todd [290] as one of the basal factors in "chronic rheumatism." He noted the transient appearance of chronic muscular or articular rheumatism subsequent to catarrhal jaundice in certain cases. Tests for hepatic dysfunction were frequently more "positive" during periodic bouts of rheumatism than in subsequent remissions. (No details and no evidence thereof were given.—Ed.)

Using the levulose tolerance test and considering a rise of 30 mg. or more above the initial level in the blood during the test as evidence of hepatic inefficiency, Miller [291] found some degree of hepatic impairment in about a third of all his rheumatic patients; in 31 per cent of 117 cases of atrophic arthritis, in 37 per cent of 41 cases of hypertrophic arthritis, in 36 per cent of 68 cases of fibrositis, in 28 per cent of 18 cases of sciatica, and in 33 per cent of 6 cases of gouty arthritis.

(He noted that Kimball (1932) found an abnormal levulose tolerance test in only one of 10 cases of chronic arthritis.—Ed.)

Vitamin C Deficiency. Subacute or chronic vitamin C deficiency produces in guinea-pigs an arthropathy which Rinehart [233] believed was markedly similar to atrophic arthritis. Synovial proliferation, pannus formation, periarticular thickening, bone overgrowth and subcutaneous nodules are produced. Superimposed infection may accentuate the pathologic process. Rinehart was unable to produce arthritis with infection in the presence of adequate vitamin C nutrition. However, when vitamin C deficiency was first produced, areas of diminished resistance to subsequent infection re-

sulted. Infection plus vitamin C deficiency more readily produced scorbutic arthropathy in animals, lesions of which resembled those of atrophic arthritis. Many of the prodromal symptoms of atrophic arthritis are characteristic of latent scurvy. Some of his patients with atrophic arthritis presented evidence of vitamin C deficiency. Rinehart therefore suggested that vitamin C deficiency may be a factor in the etiology of some cases called "atrophic arthritis."

Dietary Habits. No direct relationship between dietary habits and chronic arthritis could be found by Hall and Myers,[292] who studied the dietary habits of 40 patients with atrophic and 27 with hypertrophic arthritis and 30 controls. No striking single abnormality in diet of any one group was found. Inadequate calories were consumed by 20 per cent of those with atrophic arthritis, by 37 per cent of controls. (Excess calories were taken by 59 per cent of those with hypertrophic arthritis, by 43 per cent of controls.) "Undesirable diets" were taken by 50 per cent of those with atrophic arthritis, by a third of those with hypertrophic arthritis, and by 40 per cent of controls. Some but not all arthritic patients took carbohydrates to excess and got inadequate vitamins and minerals, but so did some of those without arthritis.

Intestinal Toxicosis. This condition causing arthritis may result according to Gutman [293] from the improper metabolism of food as well as from infection in the "pathologic colon." However, Keefer [279] found no constant deviation from normal gastrointestinal function in arthritis. Gastric anacidity, carbohydrate indigestion, and "abnormalities" in the colon are found inconsistently and no oftener than in other diseases, and there is no proof that they are significantly related to the course of the arthritis. Keefer found no gross or histologic evidence of atrophy or other disturbance in the intestines of four patients who died with atrophic arthritis.

Food Allergy. Many persons are hypersensitive to certain foods and develop acute symptoms of various sorts. Some of these patients have a coincident atrophic arthritis. It has been suggested that the arthritis is related primarily or secondarily to the food allergy (Brown, G. T.[214]); that the arthritis may be an allergic reaction to offending foods; or that an atrophic arthritis can be made worse by subsequent attacks of food hypersensitivity. No convincing evidence has ever been offered; new data are inconclusive. Among many patients Bauer [294] never saw one whose atrophic arthritis was traceable to food hypersensitivity.

Factor of Endocrine Abnormality. Many physicians speak vaguely of endocrine abnormalities associated with or responsible for arthritis, but specific data are rarely given and definite evidence that such abnormalities occur in a significantly greater percentage of arthritics than in normals or persons with other chronic diseases is not at hand. Howitt,[263] for example, considered the prodromal symptoms of atrophic arthritis "referable to

overstimulation of the katabolic group of endocrine glands, for atrophic arthritis is, like exophthalmic goiter and diabetes, a disease of the endocrine-sympathetic system." Todd [290] stated that in chronic rheumatism, "subthyroidism is frequent. . . . A pituitary factor is not infrequent. . . . Ovarian dysfunction with oligomenorrhea or amenorrhea is common in atrophic arthritis." Another [295] contributed this gem: "Experience points to a close connection between arthropathies and endocrine glands. Constitutionally the dolichomorphic type, probably governed by the anterior pituitary, thymus and interstitial gonads and influenced by the thyroid and adrenal glands is associated with atrophic arthritis, while the brachymorphic constitution, dominated apparently by thyroid, Langerhansian body and gonads, seems most frequently connected with the hypertrophic type." (There we are; its as clear as that! But to make it easier certain endocrines were recommended "whenever the condition demands opotherapy."—Ed.)

1. Alterations in thyroid function. Some consider hypothyroidism, others hyperthyroidism, causally related to arthritis and report significant deviations from the normal metabolic rate fairly frequently in arthritics. Hall and Monroe (1933) found rates below — 10 in 36 per cent of cases, and below — 17 in 18 per cent. However, Monroe[296] reported that the incidence of atrophic arthritis in 98 cases of myxedema and in 414 cases of hyperthyroidism was low, probably no more than would be expected statistically. Of the hyperthyroid patients, 3 per cent had atrophic arthritis, 2 per cent had hypertrophic arthritis, 4 per cent had arthralgia or myalgia, 1 per cent had bursitis, and 90 per cent had no joint disease. Of the myxedematous patients, 3 per cent had atrophic arthritis, 5 per cent had arthralgia and myalgia, none had bursitis, 60 per cent had no rheumatism, but 33 per cent had hypertrophic arthritis. This may have been due to the fact that the average age (51 years) of the myxedematous patients was 15 years greater than that of the hyperthyroid group, an age when hypertrophic arthritis makes its almost universal appearance.

Duncan (1932) stated that patients with preëxistent atrophic arthritis showed exacerbations of symptoms when hyperthyroidism developed, that joint pains were often associated with hyperthyroidism, and that thyroidectomy afforded marked, prompt relief to joints. Bach [297] reported three such cases. One case was detailed: that of a young woman with polyarthritis and "slight but definite signs of hyperthyroidism" which later became marked. After thyroidectomy "immediately the pains, stiffness and periarticular swelling disappeared," without recurrence.

(It is the belief of the majority of the editors that the relief experienced in some cases from thyroidectomy, parathyroidectomy and so forth is quite nonspecific, the result not of *the* operation, but of *an* operation, and that almost any surgical operation may produce similar results. Such dramatic relief is often seen in the upper extremities after lumbar sympathectomy; it is also seen after appendectomy, cholecystectomy, tonsillectomy, and splenectomy. Unfortunately the relief is usually transient, merely a brief remission having been induced. Occasionally, however,

relief is prolonged. In evaluating the effect of any surgical procedure in arthritis one must [but most writers do not] take this nonspecific postoperative effect into account. However, one of us, A. A. F., believes that the correction of hyperthyroidism may exert some "specific" influence on the course of the disease.—Ed.)

Metabolic rates were determined by Gray, Bernhard, and Gowen [269] in 47 cases of atrophic arthritis; 53 per cent gave minus readings (average — 7), 47 per cent gave plus readings (average + 14). The rate tended to drop as the disease progressed; the average rate in cases of advanced arthritis was — 9. In two cases hyperthyroidism developed; the effect of thyroidectomy thereon was not noted.

(These figures do not tell us much. It is not stated how many cases had definitely abnormal rates—over 15 or under 15 per cent.—Ed.)

Race [260] and Dawson [103] concluded that patients with atrophic arthritis show no significant deviation from rates seen in a group of normal or chronically ill persons.

2. Parathyroid dysfunction has recently been advanced as the cause of certain cases of arthritis, including the atrophic type, and particularly of ankylosing spondylitis. Parathyroidectomy is being performed.[298] The subject will be discussed later under "Relationship between arthritis and hyperparathyroidism." Suffice it to say here that Lahey and Haggart [271] found in 200 cases of atrophic arthritis no clinical, chemical or roentgenographic evidence of hyperparathyroidism.

Factor of disturbance of the sympathetic nervous system. Although several of the year's writers glibly spoke of atrophic arthritis resulting from disturbances of the sympathetic nervous system, no new data to support the idea are at hand. Disturbances of the sympathetic system have been considered responsible for the vasomotor symptoms of the disease. These symptoms can be largely cured by sympathectomy, but opinions differ as to whether the arthritis is also cured thereby. Keefer [279] stated that before one can blame arthritis on these vasomotor symptoms it must be shown that: (1) all patients have these changes prior to their arthritis; (2) vasomotor reactions are capable of producing inflammatory changes in synovia; (3) the arthritis can be arrested by sympathectomy. It was his opinion that vasomotor disturbances undoubtedly contribute to the symptomatology of atrophic arthritis, but that neither they nor other functional alterations in the sympathetic nervous system have been proved responsible for the disease, or their sole correction entirely responsible for a cure.

Relation of Atrophic Arthritis to Rheumatic Fever. This was discussed under the section on rheumatic fever.

Relation of Atrophic Arthritis to Tuberculosis. Some believe that many, if not all, cases of atrophic arthritis represent "tuberculous rheumatism," an atypical, possibly allergic, reaction induced by tubercle bacilli (Copeman [102]). The idea was discussed under "Tuberculous rheumatism." Forestier [41] spoke of an attenuated form of tuberculous arthritis of the

fibrous type, a transition type between true atrophic arthritis and what the French call " tumeur blanche." Tuberculosis was rare among Dawson's [103] 800 patients with atrophic arthritis, only three having it. Moncrieff [104] accepted the evidence that positive tuberculin reactions in arthritic children are no more numerous than one would find in a group of healthy children of the same ages.

Conclusion on Etiology. No extended comment is necessary. Obviously the cause of atrophic arthritis is unknown. At present the infectious theory remains dominant (and we feel rightly so), but it is far from proved.

Treatment.—General Remarks. Arthritis is one of the two diseases most poorly treated by physicians, according to Yater [299] who, however, found excuses therefor. Chronic arthritis requires months or years of consistent treatment, which is difficult when most patients change physicians so often. Markedly disabled, the patient may be unable to earn money for proper treatment. Little is known regarding the cause or cure of the disease, and, as to what is the best treatment, there is much confusion in the minds of general practitioners. (In the minds of some " rheumatism specialists " also, may we add.—Ed.)

Those of wide experience agree that since no " specific " for the disease is at hand, the patient and not just his disease must be treated, perhaps the patient even more than the disease. A broad approach to the problem of treatment is required, and regardless of individual opinions on the relative importance of this or that causal factor, whatever physiologic abnormality a patient presents, whatever coincident or related infection, endocrine or metabolic disturbance, or postural or occupational strain, is present should be corrected as far as possible in order to help the patient cure himself of a disease which the physician can't, or hasn't yet learned how to, cure.

This necessitates a " combined attack," but the attack is intended to overwhelm the disease, not the patient, and the latter must not be swamped by a too energetic or too inclusive treatment. The plan of treatment must therefore be individualized to suit the requirements of each patient at the moment. The program of therapy should have latitude and longitude. First will be used, not *every* accepted form of treatment, but only a selection of those measures which the stage of the disease, and the patient's psychologic make-up, constitution, and finances, warrant. In the first few weeks of a rather healthy patient's mild disease one perhaps could not well defend treatment by radical removal of foci to the extent of removing, for example, a questionably-infected gall-bladder or a hyperemic cervix. A little later, however (but not too late), when the arthritis appears formidable such measures may be defensible.

In the presence of a poor patient with an obviously subsiding chronic arthritis one could hardly defend the institution of a long and expensive course of even the most touted vaccine. In some regards nature is a poor rheumatism specialist, particularly when she fosters flexion deformities and ankyloses. But nature may be a good physician if given a chance and

helped, not hindered, especially early in the disease, when the patient is so apt to traumatize his diseased joints and to deplete his strength by sleepless nights and anxious days. When it is apparent that a benign nature has things under control, it is perhaps best for the physician to be an admiring spectator and not a too obtrusive fellow-actor. If physiologic equilibrium is being satisfactorily obtained without vaccines, it is best to hold their use in abeyance, since we know too little about the mechanisms involved and may do harm, not good. If, however, one is faced with a relentlessly progressive disease, it seems folly to withhold vaccines "because they only help one in three or four." That fourth patient deserves his chance for relief. At times, therefore, the combined use of several measures may be necessary, and the program may quite justifiably include certain fairly safe remedies which are not yet "standard."

The program of treatment must also have longitude. It must be planned so that it can be kept up over a long period of time as efficiently, and yet as inexpensively, as possible. This means substitution of at least part of professional physiotherapy by home physiotherapy, the use of the less expensive (but just as good) analgesics by mouth rather than fancily-named salicylates or other medicines by vein. The physician must foresee the probable necessity of modifying treatments to meet changing circumstances. He should be planning what to do next if in a particular case the current program fails after a reasonably, but not unreasonably, long trial period. The patient should know that the physician does have a second, third or even fourth line of defense, that other measures with a reasonable likelihood of success are available as necessary. This creates the confidence and optimism so vital to the arthritic patient. Although the physician may alter details of treatment from time to time, he will constantly impress upon the patient the importance of continuing those fundamental principles of treatment which apply to all chronic, especially infectious, diseases—the necessity of extra periods of rest, adequate diet and so on.

The array of measures suggested hereafter shows only too well that no one remedy is consistently helpful. Each must be regarded as part of a mosaic, not to be used alone or judged too much on its own merits. Herein, however, lies the difficulty in evaluating researches on treatment, for in most cases the measure used was but part of a larger plan of treatment, though the writer often fails to mention the fact. *Thus the matter of setting up controls is so difficult,* yet so important.

Infected Foci and Their Management. The controversy as to relationship between infected foci and chronic arthritis is still actively discussed.[279, 282, 300] Pemberton [253] again stated that many infected foci are the result, not the cause, of the disease. Of 300 patients with "chronic arthritis," 66 per cent of those with atrophic and 47 per cent of those with hypertrophic arthritis had had infected foci removed before he saw them. Nevertheless he found infected foci in 79 per cent of those with atrophic and in 81 per cent of those with hypertrophic arthritis. Obviously the pre-

vious removal of infected foci had either been done incompletely, or other foci had subsequently developed. Obviously, also, many were not helped by removal of such foci. However, others believe that results obtained from the removal of foci leave little doubt as to the value of this procedure, which in their opinion is the sine qua non of therapy.[300, 301] Removal of foci alone is rarely successful, and when it is to be done in the case of depleted malnourished patients, the patient should be "built-up" beforehand.[302] One should distinguish according to Sherwood [303] between unwalled-off infected foci which may produce systemic disease, and walled-off infections such as dental-root cysts, which he considers harmless.

If removal of a focus is followed by either exacerbation or disappearance of the arthritis, a relation between focus and joints is generally assumed. However, improvement following removal of foci may be due to a general "stimulation resulting from removal of one cause of a lowered resistance." [279, 282] When neither improvement nor exacerbation occurs it is assumed that the removed focus was not the cause, or that the arthritis was too established for focal removal to help. Stated reasons for doubting the theory of focal infection include: failure of improvement in arthritis after removal of foci, cases of arthritis without demonstrable foci, improvement of arthritis without removal of foci, frequency of infected foci in non-arthritics, and inability to obtain consistently the same bacteria from foci and joints.

1. Teeth. Some favor the removal of dead teeth,[282] others consider them harmless and remove only definitely infected teeth.[34, 103, 300] If many are to be removed, some remove four or five at a time, with intervals of two weeks between sessions.

2. Tonsils. Of 500 patients with "arthritis" seen by Nissen,[304] 10 per cent had had their tonsils removed prior to the onset of the disease, 90 per cent had not. The course of the arthritis in these two groups was studied. Infected tonsils should be removed only during a period of relative arthritic quiescence. If such a period does not appear, or if in a given case the arthritis is constantly progressive, Nissen believed "tonsillectomy is never indicated." (He considers "arthritis" of many types all one disease. The types are not differentiated, hence no conclusions can be drawn.—Ed.)

3. Infected sinuses. Infected sinuses including "silent sinusitis" are rarely a focus in arthritis according to some, not uncommon according to others.[103, 300] Conservative treatment should be thoroughly tried before operation.[282]

4. Nasopharyngitis of the diffuse type, even in the absence of tonsils may act as a focus (Willcox [300]).

5. Gall-bladder. That an infected gall-bladder may be the sole causative focus in arthritis, Patterson [305] concluded from observations on one patient who noted prompt relief on two occasions, once after an appendectomy and (presumably) a cholecystostomy (with subsequent relief for eight years), and again after cholecystectomy. Nonhemolytic streptococci

were found in the gall-bladder, a vaccine of which produced joint symptoms. (Although prolonged remissions were obtained after both operations it is still possible that relief was due to a non-specific postoperative effect.—Ed.)

6. Uterine cervix, and prostate gland. Infection of these is in most cases responsible, according to Robinson [306] for arthritis. He noted consistent improvement only when these (and not other infected foci) were treated. "There is no remedy for it except (long-wave) diathermy given intrapelvically by special electrodes."

7. Secondary colon infections. These according to some [293, 300] are frequent, according to others rare.[307] Their importance is often exaggerated.

Bacterial Vaccines, Antigens, Filtrates. Of those writers who have recently expressed an opinion on vaccines, about 60 per cent have favored their use, 40 per cent have not. Milliken [308] gave to 25 patients with "chronic arthritis" a mixed vaccine (streptococci from blood, tonsils and colon added to Clawson and Wetherby's vaccine). An average of 36 injections was given over an average period of four months. Systemic reactions were avoided, small doses used. Patients were treated until they remained symptom-free for at least 30 days. "Complete relief" was obtained by 12 patients (48 per cent); the average duration of their disease was 30 months. "Moderate relief" was obtained by eight patients the duration of whose arthritis averaged 69 months. Five patients (20 per cent) who had had the disease on an average of 106 months received little or no relief. The best results were obtained in early cases and by those with the greatest tolerance for the vaccine. (No other treatment was mentioned. The series is very small, no controls were used, and the "arthritis" was undifferentiated.—Ed.)

Intravenous injections of streptococcal vaccine from strains to which patients were "skin-sensitive" were given by Wainwright [278] to 45 patients; 30 (66 per cent) were "improved." Desensitization was attempted by using very small doses. Constitutional reactions were avoided, but focal reactions in joints were common. Improvement was slow but generally progressive and was first noted in four to six weeks. Agglutinins increased, and skin-sensitivity diminished or disappeared. The sedimentation rate was variably affected in those who improved, steadily dropping in some, and remaining elevated in others despite definite objective and subjective improvement. Hence Wainwright considered it of doubtful value as a test of improvement.

Sherwood [303, 309] reported further experiences with vaccines. An earlier series consisted of 674 cases of "arthritis" ("atrophic or periarticular" 311 cases, "rheumatoid" 32 cases, hypertrophic arthritis 260 cases, gonorrheal 19 cases, and a few cases of neuritis and myalgia). About 60 to 70 per cent of patients in each group were "markedly improved." Treatment of four different types was "almost wholly with vaccines": Clawson and Wetherby's (Lilly Streptococcal Vaccine), Cutter's mixed respiratory vac-

cine, and two modifications of the latter. Results with each vaccine were about the same. (Sherwood's "rheumatoid" cases were apparently those of early atrophic arthritis "with no bony change." No comparisons were made with patients treated by other methods than the use of vaccines.—Ed.) Sherwood later treated 300 "arthritic" patients, of whom 100 each were treated with "Cutter's arthritis vaccine," with a casein solution, and with physiologic saline solution. Patients were assigned the solutions in rotation, the contents being unknown to the administrator. Within eight weeks (a very early time—Ed.) "marked improvement" was noted by two-thirds of those treated with vaccine, by half of those with casein, and by a third of those with saline; relief by the last-named measure was regarded as from mild psychotherapy.

Streptococcal vaccines were approved by several.[250, 251, 274, 307, 310] Gray [251] found low complement in patients reacting unfavorably to minute doses. Various vaccines and antigens were given intravenously and subcutaneously by Boots,[34] Dawson,[103] Holbrook and Hill [302] without striking differences in results with different vaccines or in controls. They concluded that vaccines are of unproved value, generally harmless, have a psychotherapeutic value, and serve to bring the patient to the physician's office for more important therapy and control. Results vary with the enthusiasm of the user. Kinsella's [33] results were "unimpressive." Of 21 European physicians who had used "specific vaccines" Slocumb [99] found only nine who were continuing them. Yater [299] thought that general practitioners should not be encouraged to use vaccines for arthritis lest they neglect more valuable methods.

Long-continued vaccine therapy was considered by Reiman and Eklund [311] to be the cause of amyloidosis in the case of a young arthritic who died of uremia after having received 41 injections of vaccine in 22 months. His blood protein was 4.71 gm., albumin 0.74 gm., globulin 2.67 gm. per cent, fibrinogen 1.29 gm. per 100 c.c.

(Parker and Keefer [256] noted amyloidosis as part of the secondary pathology of the disease. Therefore, the disease and not the vaccine may have caused amyloidosis. —Ed.)

The failure of autogenous vaccines to help more than 48 per cent of their patients led Lamb, Anderson, and Nerb [312] to use filtrates (antivirus) of autogenous streptococci to which patients were "skin-sensitive." Of 70 patients with atrophic arthritis, 13 per cent "recovered," 36 per cent "greatly improved," 36 per cent improved slightly, 15 per cent were unimproved.

(No controls treated without vaccine or filtrates were studied.—Ed.)

Intravenous doses of urinary proteose from arthritic patients gave no encouraging results (Kinsella [33]).

Foreign Proteins. The actions and uses of, and contraindications to, foreign protein therapy were reviewed by Hektoen [313] and Cecil [234] who

regarded this treatment in selected cases as distinctly useful even if not brilliant. It generally does no harm although it may do no good. Cecil believed that foreign proteins should always be tried in acute arthritis unrelieved otherwise. Many of his early patients with atrophic arthritis "remained well" thereafter; many with chronic arthritis were definitely improved. Other authors [34, 103] considered it of doubtful value.

Diet. Pemberton [253] again stressed the value of a diet adequate in proteins, vitamins, and calories, but with a reduction of concentrated carbohydrates. "There is some evidence to suggest that in selected cases a difference of 300 calories might turn the scale in favor of retrogression or improvement." He and Scull [314, 315] considered that the value of their diet was explained by the fact that one of the dynamic pathologic changes in atrophic arthritis is a disturbance of water distribution in tissue, exemplified by the common appearance of edema in periarticular tissues. Their diet tended to provoke a negative water balance, which reduces swelling and inflammation.

(These water-balance studies were calculated only semi-quantitatively. The total acid-base balance and the insensible perspiration were not fully determined.—Ed.)

Considering the edema of arthritis as due to a low plasma albumin, Davis [29] regarded protein restrictions as harmful. A generous intake of protein may lessen the edema.

To correct supposed hepatic dysfunction in atrophic arthritis Todd [290] "spares" the liver by prohibiting all fats (except butter and oils) and lactalbumin. (No acceptable proof of the need or value of this diet was given.—Ed.)

A diet high in "protective foods" (fresh fruits and vegetables), but moderately low in proteins and calories and low in carbohydrate, was used by Langstroth.[316] Others thought that a low-carbohydrate or low-protein diet did more harm than good (Boots [34]). Lookie [29] found restriction of carbohydrate of no merit and excesses of carbohydrate apparently not harmful; several patients continued to improve despite a daily intake of 500 gm. for 15 to 65 weeks. The administration by Hench [29] of 400 to 600 gm. of carbohydrate daily for many weeks to patients whose atrophic arthritis was temporarily inactivated by jaundice did not counteract the analgesia with jaundice nor bring out symptoms of arthritis. Studies by others (Bauer,[294] Hall and Myers [292]) did not indicate any abnormality in carbohydrate utilization or suggest that excess carbohydrate intake was an important factor. They saw no theoretical or clinical value in a low-carbohydrate diet.

(Our opinion is divided on this point. The majority agree with the foregoing views. Others believe that disturbed nutrition forms the background of much ill health from infection and that almost all nutritional deficiency states are best controlled by carbohydrate restrictions. Hence, they favor the view that nutritional disturbances are a causative factor in atrophic arthritis.—Ed.)

The majority favor no particular dietary restrictions, prescribe a generous intake of food except when reduction of the trauma due to obesity is

required, and believe that most patients do badly on prolonged dieting or starvation.[29, 34, 106, 292, 294, 301, 302, 310]

Excess feeding of vitamin C was advocated by Rinehart [233]; improvement in capillary resistance tests (an index of latent scurvy) and in joints was noted. However, such feedings by Faulkner [225] for four weeks were not helpful. Some believed vitamin deficiency played no rôle in the disease.[292, 294] The results obtained by Bauer's patients [29] who adhered to a high-vitamin diet for three to five years were no better than those seen in his patients who had not been so treated.

For weak patients, a high-calorie diet and insulin just before meals are prescribed for a month by Copeman [301] (15 units once daily) and by Eaton [317] (5 to 20 units three times a day).

Additional Intestinal Therapy. Colonic irrigations are still recommended by some, and condemned by others.[34, 252, 293, 299, 318] The reported abnormalities in intestinal configuration were not found in 50 cases by Lang.[250] There is no evidence that these "abnormalities" (if they really are abnormalities) are related to atrophic arthritis. Possibly they result from (any) chronic illness.[279, 294] Wyatt [307] found no consistent evidence of faulty elimination. Cathartics can be replaced by exercise, regular habits, diet, and simple lubricants.

Iron; Blood Transfusion. Only two of 21 anemic patients of Collins [268] responded well to massive doses of iron. Transfusions may improve those with acute or subacute arthritis, with or without anemia, but are of little value in chronic afebrile cases.[251, 301, 302, 307] Intragluteal injections of leukocyte extract improved Hartung's patients.[29]

Miscellaneous Substances. Cinchophen derivatives are very useful drugs which have been condemned unjustly, according to Snyder [29] and Eaton [317] who noted no significant toxicity therefrom. In the present state of our knowledge no endocrine therapy is specifically indicated.[103] Nadler [319] warned against the use of dinitrophenol in arthritis; peripheral neuritis and multiple joint pains may result.

Gold Salts. Gold salts are given in various preparations; solganol (aurothio-glucose), allochrysin (sodium aurothiopropanol sulphonate), myoral, sanochrysin, myochrysin (gold sodium thiomalate), gold thioglycolate, or gold sodium thiosulphate (crisalbine). Some are given intravenously, others intramuscularly in aqueous solution or oil suspension. Colloidal gold, gold chloride or gold cyanide are ineffective (Forestier [41]). Contraindications to gold are the presence of severe diabetes, nephritis, hepatitis, marked hypertension or hemorrhagic tendencies. Doses are usually given weekly until a total of 1.5 to 2 gm. is given. Some give only one course, but Forestier stated "no case of rheumatoid arthritis has ever been cured by a single series of injections." According to him at least two courses are always necessary, with an interval of not more than six to eight weeks between.

Many patients are sensitive to gold and reactions are common. Focal

reactions include increased joint pain and swelling. Mild general reactions include fever, urticaria, pruritus, "gold bronchitis or flu," herpes. They may not necessitate cessation of treatment. Severe and occasionally fatal reactions may occur as skin and mucosa, liver, kidneys and blood cells are affected. Symptoms are erythematous rashes, occasionally exfoliative dermatitis, albuminuria, hematuria, or acute nephritis with uremia, stomatitis, jaundice and severe hepatitis, iritis, vomiting, hiccough, and diarrhea (Abdel-Sayed,[262] Forestier,[41] Hartfall and Garland,[320] Holmes,[321] Slocumb,[99] and Slot [42]). Agranulocytosis and fatal hemorrhages have been noted (Poynton [229]). One patient was delirious for two weeks (Abdel-Sayed [262]). Holmes [321] heard of two fatalities and had one patient recover from severe dermatitis. Of 100 patients treated by Hartfall and Garland three died of exfoliative dermatitis. Sixteen of 21 "rheumatic" patients treated with gold developed, after one or two injections, punctate basophilia and polychromatic blood cells which sometimes persisted 10 months.[322] In spite of these marked and even fatal reactions, however, some frankly considered gold the most effective treatment of the disease.[41, 42, 320] Gold must be given carefully to selected patients by physicians alive to its dangers. Of Abdel-Sayed's [262] 14 patients, six were "cured," five improved. Of 100 patients of Hartfall and Garland's [320] 70 per cent were "apparently cured or markedly improved." Pemberton [323] (Liverpool) treated 69 patients: 18 per cent were cured, 40 per cent much improved, 32 per cent improved. Forestier [41] treated 550 patients; "between 70 and 80 per cent responded favorably." Fifty per cent of patients with early arthritis and 20 to 30 per cent of those with old arthritis were "apparently cured" by two to five series of injections, and they remained so for two or three years without other treatment.

(None of the editors has used this method. Untoward reactions have appeared often enough to make one very conservative regarding it. No other current nonsurgical treatment for arthritis (including fever therapy) has a mortality of 3 per cent, which is that of one series. Results would have to be unquestionably superior to warrant this risk. No control series were reported by most of the writers. Many patients had supplementary treatment which was frankly discounted.—Ed.)

Sulphur. It is claimed that injections of colloidal sulphur elevate the cystine content of nails to normal, reduce the sedimentation rate, and improve the joints in the majority of cases. Sulphur is injected intramuscularly, intravenously, or both. Rawls, Gruskin and Ressa [284] treated 200 patients with "arthritis." Some who did not respond to small doses (10 mg. twice weekly) obtained results from 20 to 30 mg. twice weekly. A few showed evidence of an overdosage after intravenous but not after intramuscular injections, the symptoms being fatigue, headache, drowsiness, anorexia, and increased joint pain. Greater toxicity temporarily developed in a few cases: urticaria and erythema, nausea, vomiting, cramps, diarrhea, and chills and fever; however, these soon disappeared. Of 33 patients with

atrophic arthritis, 15 were "improved." Those with a low cystine content of the nails received the most benefit. Some were previously given a placebo (Ringer's solution intravenously) for six to eight weeks; improvement with sulphur was greater.

Wheeldon [255] treated 892 patients with "chronic arthritis" with sulphur. He reported results in 25 cases each of atrophic and hypertrophic arthritis resistant to other therapy. Each patient received 40 intravenous and 40 intramuscular injections of "Sulfur-Diasporal." "Every case improved subjectively." Muscle spasm was reduced in 85 per cent, and joints became smaller in 65 per cent, many becoming more movable. Detailed studies were made on the physiologic effect of sulphur on the cystine content of nails, sedimentation rate, blood count, sugar and calcium, urinary indican, blood pressure and weight.

Woldenberg [285, 286] treated 231 patients with atrophic arthritis. "Every case showed excellent clinical improvement." Best results were from 30 mg. of colloidal sulphur (Sulfur-Diasporal) intravenously daily for 10 days. "In the majority of cases patients were free from pain after five or six injections." Sometimes in acute cases a dose of 30 mg. intravenously "completely rid the patients of the intense pain they were suffering within 36 hours of the first injection." "So far as we know no recurrences of the disease have taken place." (It is difficult indeed to believe these extravagant statements, particularly in view of the more conservative reports of others. The patients also received physiotherapy daily. No control series was observed and no details of the follow-up are given.—Ed.)

Of 11 patients who were given an average of 60 c.c. (600 mg.) of colloidal sulphur (sulisocol) intravenously by Sashin and Spanboch,[324] six "improved," five did not. No conclusions were drawn. McCarty [325] found sulphur "helpful in a small series of cases." Todd [290] approved such therapy. However, Kinsella [33] noted no definite improvement in 50 to 60 patients, and in 12 cases of Dawson [103] it was "absolutely without effect."

Choline and Histamine. These substances are being applied by iontophoresis to produce pronounced local and mild general vasodilation without the unpleasant systemic reactions from their parenteral use. After iontophoresis with mecholyl (acetyl beta methylcholine chloride) such an effect lasted six to 10 hours, according to Abel [326] who treated 11 patients with atrophic arthritis; 10 were "definitely improved." Two patients with Strumpell-Marie's disease were not benefited. Kovacs [327] regarded mecholyl iontophoresis the method of choice in the local treatment of small joints in cases of atrophic arthritis. During iontophoresis the drug is actually absorbed; resultant physiologic effects on dogs were demonstrated by Kotkis and his associates.[328]

Producing less vasodilation, mecholyl is inferior to histamine, according to Kling [17] who tabulated reported results of histamine iontophoresis for "rheumatic affections": of 730 patients 84 per cent were "cured or improved." Kling treated 12 patients with "spondylarthritis and radiculitis";

seven improved. Of eight patients with "sacroiliac arthritis" two improved; of eight with atrophic arthritis seven improved after 10 to 20 applications. Treatments were sometimes repeated for recurrences of the disease. Smaller joints responded better than large joints. Copeman [801] approved the use of histamine by subcutaneous injection as well as by iontophoresis. For unstated reasons "active rheumatoid arthritis" was considered a contraindication. Levant [329] checked the physiologic reactions of iontophoresis with histamine against that with controls (tap water and four other solutions). All produced superficial hyperemia, but therapeutic results were obtained only with histamine. Several patients with "arthritis" were benefited. (In most of these papers the classification of arthritis was completely inadequate. Practically no control studies were made on patients treated otherwise. —Ed.)

Harpuder [330] demonstrated the production of vasodilating substances (histamine and acetylcholine) in the skin during physical therapy.

Concentrated Viosterol: Vitamin D in Massive Doses. Two arthritic patients on massive doses of vitamin D for hay fever, as prescribed by Rappaport and Reed (1933, 1934), noted improvement in their joints. Dreyer and Reed [331] therefore gave similar large doses to arthritic patients. Of 34 patients with atrophic arthritis, 25 were "improved." Patients with hypertrophic arthritis and with "arthralgia" were also improved. Improvement was first noted, in some cases, after a week, in others after six months' treatment. The disease was apparently "controlled," not cured, for although many became symptom-free and had no recurrences in 18 months, others had mild recurrences when administration of the drug was stopped. Patients were given doses of 200,000 U.S.P. or international units of vitamin D (concentrated viosterol) daily for one month. If relief was noted the dose was never increased; otherwise, the dose was increased by 50,000 to 60,000 units each week until improvement or overdosage was noted. In stubborn cases patients were given 600,000 to 1,000,000 units daily for a few days and then put back on 200,000 units daily. The majority received relief on 300,000 to 500,000 units daily.

Tolerance of patients to the drug varied greatly. Toxicity occurred more often after prolonged use of smaller, than the short use of larger, doses. Symptoms of toxicity were persistent nausea, frequency of urination (with or without polyuria), lassitude, anemia, polydipsia, diarrhea, vomiting, and abdominal pain. Blood calcium sometimes rose to 25 to 30 mg. per 100 c.c. often without symptoms. To prevent or combat toxicity, 6 gm. of brewers' yeast were given three times a day with frequent success. When signs of toxicity appeared, administration of the drug was discontinued for two weeks with disappearance of symptoms. Then the drug was continued in nontoxic doses. Conclusions from studies on humans and animals were that concentrated vitamin D in the doses used is not hazardous if signs of early toxicity are recognized and the drug is stopped. Persistence in administration might lead to permanent effects, even death.

Patients on this treatment for two to five years for other diseases showed no hypertension or other ill effects. (The report is conservatively written, but apparently controls were not studied. Since a "control" and not a cure was obtained, auxiliary treatment such as physiotherapy was advised. In a recent communication Reed [212] stated that they are now using no more than 300,000 or 400,000 units daily. Vrtiak and Lang [332] have treated 20 patients with atrophic arthritis; 12 [60 per cent] were improved, 8 were not. Results were considered not unlike those with other methods and indicated that a conservative attitude toward such therapy should be adopted.—Ed.)

Rest and Movement. The virtues of systemic rest have been stressed as the most important part of treatment.[251, 253, 333] Prolonged rest in bed is necessary for acutely swollen joints, for which splints or casts may also be required to make rest absolute. In chronic cases the problem is not one of rest versus exercise but of rest and exercise. The patient may overdo on rest, with resultant atrophy and ankylosis, but the majority overdo on exercise to "keep the joints limber." [307, 318, 334] In chronic cases some exercises, including bed-exercises, are necessary to preserve joint function and muscle tone, but not that amount which causes more pain.[252] Therapeutic exercises for various joints were described in detail by Coulter and Molander.[335]

Physical Therapy. Medicines, vaccines, and diets for arthritis gain and lose their popularity but centuries of use have proved the value of physical therapy. Many physicians do not understand its advantages, hence there is a scarcity of trained physiotherapists. In Massachusetts there are about 22 arthritic patients for every physician, but about 70,000 patients receive no treatment whatever (Ober [29]). Physiotherapy is justly or unjustly held in disrepute for reasons listed by Behneman.[336] Indications for, and methods and results obtainable by physical therapy have again been reviewed.[337, 338, 339, 340, 341, 342] Whenever possible the arthritic patient should receive physical therapy in three ways: (1) by daily home measures used by the patient himself [335, 343]; (2) professional physiotherapy three or more times a week from technicians or physicians trained therein; and (3) annual or semi-annual visits to a spa or other institution for treatment combined with the advantages of a vacation (Aldred-Brown,[344] Holmes,[345] and Lautman [333]).

To supplement the limited sessions of professional physiotherapy which patients can afford, the intelligent ones and their relatives should be fully instructed in simple home methods. Thus the cost of the patient's care can be reduced and the physician can control the patients over long periods necessary for treatment. By demonstrations and mimeographed sheets Coulter [29] teaches his patients optimal types and amounts of heat, massage and exercises, and the use of cheap but effective electric bakers, whirlpool baths and appliances for harmless exercises.

(Few spas attempt to teach patients simple home methods of physical therapy which would permit their advantages to be projected into the patient's home environment. Seventy-five per cent of patients seen by one of us had previously consulted

cultists, generally because little or no physiotherapy was prescribed by physicians. Unless the better types of professional and home physiotherapy are more fully utilized by physicians, patients will continue to flock to the spine and foot twisters. —Ed.)

Before " home-physiotherapy " can be safely prescribed, physicians themselves must learn its principles and methods, and when it is given it should always be under a physician's general supervision (Ober [346]). Uses and physiologic effects of heat were thoroughly reviewed by Pemberton [347] and Fox.[348] Diathermy, approved by many, may be harmful in cases of atrophic arthritis with much demineralization of bone, according to Holbrook and Hill.[302] (No proof of this is given.—Ed.) Pelvic diathermy is particularly useful for pelvic foci of infection (Robinson [306, 349]). Cold or hot Epsom-salt packs are often very analgesic.[302] Hot paraffin packs deserve wider use.[302, 307] Thermal baths and douches, and Fango (mud) packs have their protagonists.[350, 351, 352] Short wave therapy for chronic arthritis was approved by several (Berry,[353, 354] Bierman and Schwarzschild,[18] Kobak,[80] Torbett,[79] Wilson [355, 356, 357]). The effect of short wave diathermy is about the same as that of ordinary (long wave) diathermy, according to Kovacs,[327] but the former can be used in regions where electrodes cannot well be applied. Kling [78] tabulated reported results from short and ultra-short wave therapy for " chronic arthritis "; of 146 patients 80 per cent were improved. Of his own 29 patients 72 per cent were improved. Results were best with the 23 meter wave.

Heliotherapy is often harmful for patients with rather acute arthritis or with fever. Dizziness, nausea, vomiting and fever may result (Holbrook and Hill,[302] Jones [334]). Massage is over-rated and alone is useless, according to Jones [334]; others stress its importance. Physical exercises can be reproduced easily and painlessly by sinusoidal currents.[334] Underwater therapy offers an unequalled means of preventing and correcting adhesions and of increasing muscle and joint function.[333, 358, 359, 360] Occupational therapy has special advantages distinct from those of physiotherapy.[361]

Roentgen Therapy. Results of roentgen therapy in " acute and chronic non-specific infectious arthritis " were " gratifying " according to Garland,[40] although not as striking as in gonorrheal arthritis. Nine patients with " acute infectious arthritis " were treated: four became symptom-free, two improved. Of 13 patients with joints irradiated in these cases, six became symptom-free, two improved. Three patients with " chronic infectious arthritis " were treated: two became symptom-free. Of 10 joints treated, three became symptom-free, six improved. Scott [362] approved radiotherapy, but King [363] considered it of little value. An analgesic, not a curative effect, is more frequent in acute than in chronic cases.

Fever Therapy. Results of fever therapy for atrophic arthritis have been satisfactory to some (Kobak [74]), disappointing to the majority. They are not nearly as good as in gonorrheal arthritis. Hench, Slocumb and

Popp [48] tabulated results given in the first 15 reports thereon (1931–1934): of 147 patients, only 7 per cent were "cured" or completely relieved. Of 60 patients treated by Hench, Slocumb and Popp, none was cured, 18 per cent were markedly, and 12 per cent moderately benefited, and 70 per cent received little or no relief. At the Fifth Annual Fever Conference (May 1935) results in 129 more cases were reported (Hefke,[45, 51] Stecker,[45] Strickler,[45, 53] Tenney and Snow [45]). Summarizing all published reports, the earlier optimistic and later conservative ones, Hench [56] found that of a total of 315 patients with chronic atrophic arthritis treated by fever, only 5 per cent became symptom-free; 25 per cent were notably relieved, but the rest received little or no relief. Results were a little better in cases of acute atrophic arthritis: of 21 patients, 10 per cent seemed completely relieved, 40 per cent notably benefited.

Recently Short and Bauer [54] gave 71 fever sessions with general diathermy to 25 patients; 80 per cent showed temporary improvement, but in only 20 per cent was this maintained until the follow-up 6 to 41 months later. None were harmed but all looked on it as a harrowing ordeal. Balancing results against the treatment's severity, Short and Bauer concluded that it was only occasionally justified and should not be used to the exclusion of other treatment. Rogers [364] noted benefit in one case. The use of low temperatures (101° F. for 3 to 5 hours) was recommended by Atsatt and Patterson.[47, 73] Simpson [45] and Shands [45] felt that artificial fever therapy given just before or after orthopedic manipulation of deformities increased the results of manipulation.

Malarial (fever) therapy was given to 13 patients by Cecil, Friess, Nicholls and Thomas.[365] All received immediate, sometimes striking, benefit, but, six months later, only one was symptom-free, a patient whose arthritis was of only four months' duration. In 12 cases the arthritis relapsed, in eight completely, to its original state; in four partially. (One of us, P. S. H., gave malaria to a patient with severe atrophic arthritis in 1928: only a temporary, partial remission resulted.—Ed.)

Surgical Procedures. 1. Sympathectomy: Sympathectomy was performed in five cases of "chronic arthritis" with hyperhidrosis and vasomotor disorders in affected limbs. Results were reported by Ross.[366] Two of three patients whose arms were affected "derived great benefit." In one of two patients whose legs were affected "the treatment was successful in relieving pain and restoring function." (No further details were given.) De Takats [367] considered sympathectomy of unproved value in chronic arthritis. In an unstated number of Boots' cases,[34] poor, as often as good, results were obtained. Unilateral lumbar sympathectomy was performed by Kinsella [33] in "about 35 cases" to study results on one leg. The first results were very good, but subsequent results did not justify continuance of the procedures. Relief of pain and increase of motion were not constant. Several papers on physiologic reactions after sympathectomy are of interest.[368, 369, 370, 371, 372]

2. Splenectomy was recently performed in two cases of "Felty's syndrome" (Hanrahan and Miller, 1932; Craven, 1934); only temporary improvement was noted. Miller and Craven have since notified Fitz [265] that the patients died 14 and 18 months after operation.

3. Thyroidectomy is said to benefit the joints of arthritic patients with hyperthyroidism. (This relationship has been discussed previously.—Ed.) Bach [297] noted marked improvement in one case immediately after operation.

4. Parathyroidectomy. Also previously mentioned was the supposed relationship between the parathyroid glands and polyarthritis and the reported relief of arthritis by parathyroidectomy. Schkurov [298] performed this operation in 83 cases of "chronic rheumatic polyarthritis and spondylarthritis." The results and other reports concerning arthritis and the parathyroids will be discussed later.

5. Orthopedic procedures. Synovectomy is done by some orthopedists for active polyarthritis, by others only for persistent monarthritis of knees unresponsive to other treatment. Radical synovectomy of knee joints may remove an infected focus and pathologic débris which interferes with partial restoration of function. Ankylosis rarely supervenes. Restoration of considerable function resulted in the few cases currently reported.[15, 19, 252, 373, 374] Several reviewed the indications, methods and results obtainable by various procedures for the correction and prevention of deformities: traction, casts, splints and supports, tenotomies, osteotomies, capsulotomies, arthroplasties, fusions, manipulations.[19, 20, 21, 152, 153, 318, 334, 374, 375, 376] Manipulation is particularly emphasized as a valuable method used insufficiently.[19, 318, 377, 378, 379] Reconstructive surgery is not indicated until the arthritis has been inactive at least six months.[334] A chair for patients with bilateral ankylosis of hip joints was described (Kuhns [380]).

Prognosis, Remissions and Results of Treatment. A patient with atrophic arthritis (or any other kind) will follow one of four life courses according to Nissen.[381] Of 500 cases of arthritis studied by him from the onset of the disease until the patient "ended with 'hic jacet'," 208 cases were classified "rheumatoid-genuine arthritis with actual destruction, partial or complete." Of these cases only 2 per cent followed course A (an initial attack and full recovery to the former level of activity); 32 per cent followed course B (remissions, relapses, and a slow steady decline in functional activity); 56 per cent followed course C (a drop to a low level of functional activity in a variable period of time, the patient remaining at that low level for the rest of his life); 10 per cent followed course D (a steady downward course from the onset of disease to death).

According to Dawson [103] about 25 per cent of patients "recover," 50 per cent "improve" or their condition becomes "quiescent," and 25 per cent become progressively worse. Of Pemberton's [253] 300 patients with atrophic and hypertrophic arthritis (types not analyzed separately), 6 per cent were "cured," 32 per cent "greatly improved," 57 per cent "definitely improved."

"The figures were almost exactly the same for both the atrophic and hypertrophic types of arthritis." Results for Lang's [250] 100 patients were: 60 per cent improved, of which 43 per cent were "markedly improved." The patient's coöperation in treatment is of paramount importance. Of those who improved markedly, 90 per cent were persistent and coöperative in treatment; of those who did not improve, 64 per cent were uncoöperative, discontinuing treatment within six months.

As a rule atrophic arthritis becomes inactive relatively slowly (within weeks or months) even under the most successful treatment. Neither preliminary nor final remissions appear abruptly within a few hours. Particular significance may therefore be attached to the dramatic sudden remissions that may accompany intercurrent jaundice. Hench (1933–1934) reported the "analgesic effect" of intrahepatic jaundice on 16 patients with atrophic arthritis, fibrositis and sciatica. Since then he has studied many more such cases in which sudden remissions accompanied jaundice of different types.[49] An example was given: a woman, aged 49 years, had periarticular fibrositis and atrophic arthritis for three years, which developed so that she was unable to turn a doorknob, squeeze a wash cloth, or grasp a tumbler. A febrile laryngitis developed for a few days. Ten days later she awoke to find herself jaundiced and completely free of all signs and symptoms of rheumatism. Details concerning the physical and chemical examinations during the remission were given. For several months the patient was completely free of symptoms, then the disease began to return. In the majority of such cases the remission was complete and lasted weeks or months, occasionally longer. These observations indicated to Hench that the clinical pathology of atrophic arthritis is probably much more reversible (and more rapidly so) than was heretofore evident, and led to the hope that an intensive study of this phenomenon may eventuate in a method of treatment similarly dramatic and prompt.

Hypertrophic Arthritis

Definition. Most roentgenologists who see any overgrowth of bone in roentgenograms in a case of articular disease make a diagnosis of "hypertrophic arthritis," and if bone overgrowth is absent, the diagnosis is apt to become "atrophic arthritis" (Pemberton [29]). Radiologists must exhibit a more informed type of scrutiny and become familiar with the variable pathologic and clinical aspects of the different arthritides to interpret roentgenograms more correctly. The clinical definition of "hypertrophic arthritis" is (or should be) quite different from the radiologic definition of "hypertrophic arthritis." Roentgenographically there are several different types of hypertrophic arthritis, such as that seen in certain traumatized joints, or those types found in certain stages of gouty, gonorrheal, atrophic and other forms of arthritis (Haden,[29] Doub,[11] McMurray [10]). To the clinician, however, hypertrophic arthritis means (or should mean) one particular disease, one special type of arthritis. The various forms of arthritis in which the roentgenographic changes of hypertrophy of bone are

but a minor feature, an incident compared to more obvious clinical features (acute trauma, acute gout, gonorrhea, and so forth), might be called "secondary hypertrophic arthritis." Thus they are distinguished from "primary hypertrophic arthritis," the clinical syndrome synonymous with "senescent," "degenerative" or "osteo-arthritis" in which, in the absence of a known cause or more striking clinical features, roentgenographic alterations constitute the most consistent and outstanding feature of the disease and give it a name (Haden [29]).

Incidence. Studies of knee joints of persons from the first to the ninth decade of life indicate that after the age of 30 years the degenerative changes that lead to hypertrophic arthritis were found with increasing frequency, so that by the fifth decade all knee joints were so affected (Keefer [382] also 1933, 1934; Bauer and Bennett [29] also 1933).

(Radiologic and pathologic studies by others have indicated that hypertrophic spondylitis is also present in practically all patients aged 50 years or more.—Ed.)

The sex incidence is about equal (Dawson [103]), but the fingers, knees and cervical spine are more commonly affected in women, the lower part of the spine and hips in men.

Symptoms and Course. Although the disease is almost universal in persons more than 50 years of age, only about 7 to 10 per cent of its victims have significant symptoms (Keefer, Parker, Myers and Irwin, 1933, 1934). Those with symptoms fall into three groups: (1) the obese, whose traumatized weight-bearing joints early proclaim their hypertrophic arthritis; (2) mechanics and workers in occupations in which trauma elicits painful symptoms; (3) hypersensitive persons (generally females) whose pain perceptions are augmented (Hench [106]). Symptoms rarely appear before the age of 40 years, usually after the age of 50. They may appear before the age of 40 in females who have experienced a premature or artificial menopause or in persons subject to some unusual forms of long continued trauma (Dawson [103]).

Symptoms are not always confined to joints. Just as every case of atrophic arthritis has some associated fibrositis, so in hypertrophic arthritis, fibrous tissue may share the pathologic process of degeneration (Howitt [263]). Neuritic and muscle pains and stiffness ensue.

(Symptoms of this senile fibrositis—fatigue, loss of muscular resiliency, chilliness and vague muscle pains—are so universally present in senility that Pennington, 1934, was of the opinion that "senility is practically synonymous with fibrositis."—Ed.)

Small gelatinous cysts occasionally appear, attached to tendons near a Heberden's node (Hench [106]). They are often opened "to let matter out." This is generally unnecessary; they may recede spontaneously. Occasionally they become inflamed. After they are opened, the walls collapse and the unsightly nodule recedes, though it may reform.

(These have escaped general notice and description. Photographs of them are in reports of Hench [106] and of Nachlas (1932). The latter studied 28 specimens thereof, generally over the terminal phalangeal joints of hands affected with Heberden's nodes. In one of Hench's cases the cystic nodule was over a midphalangeal joint. According to Nachlas the mucoid or gelatinous material therein may contain excess calcium in solution but no urates, and if unremoved, the nodules eventually solidify to form genuine bony Heberden's nodes.—Ed.)

Roentgenograms. Radiologic features were reviewed by Doub.[11] As before noted, those seen in cases of "traumatic hypertrophic arthritis" in young persons subjected to severe acute or chronic trauma may resemble those of "senescent hypertrophic arthritis" (degenerative, osteo-arthritis) in relatively non-traumatized joints of the elderly (e.g., distal phalangeal joints). Cases of polyarticular "hypertrophic arthritis" are more likely to represent senescent hypertrophic arthritis than cases of chronic monarticular "hypertrophic arthritis," as these latter may represent old traumatic arthritis, such as ensues in hips after Perthe's disease or osteochondritis or following slipped femoral epiphyses in childhood.[10, 11] Thus the average age in McMurray's [10] cases of bilateral hypertrophic arthritis of hips was 53 years; in cases of unilateral hypertrophic arthritis of a hip it was only 34 years and there was a frequent history of childhood injury. Therein lies further evidence of the necessity for distinguishing between the clinical syndrome of (senescent) hypertrophic arthritis, which is one disease, and "hypertrophic arthritis" in the radiologic sense which is not a disease per se but a radiologic feature of several diseases.

Pathology. The articular pathology in hypertrophic arthritis, reviewed by Keefer [382] and Parker and Keefer [256] was so different from that of atrophic arthritis that the idea that the two diseases are the same seemed untenable. Muscles, tendon sheaths and fascia, with their small blood vessels, also participate with joints in the general state of fibrotic thickening, according to Howitt.[263]

(The pathology of this associated "senescent fibrositis" is not described further. As has been done for joints, studies on the histology of muscle and fibrous tissue at different age periods should be made to clarify the pathology of senescent, as contrasted to other types of, fibrositis, and to explain the "stiffness of age"—Ed.)

Laboratory Data. Marked anemia is not a feature of hypertrophic arthritis. Gray, Bernhard and Gowen [269] found the erythrocyte count below 4,000,000 per cu. mm. in only 16 per cent, and the value for hemoglobin below 70 per cent in only 6 per cent, of cases of hypertrophic arthritis. Hemoglobin was normal (over 14 gm.) in 11 of Collin's [268] 23 cases, between 12 to 14 gm. in 11 cases, below 10 gm. in only one case. The Schilling count was shifted to the left (an increase in percentage of younger neutrophiles) in only 17 per cent of Steinberg's [270] cases of hypertrophic arthritis, but in 78 per cent of his atrophic cases. The percentage of younger neutrophiles was less than four in most cases of the former, above four in most of the latter. There was a general correlation between Schil-

ling counts and sedimentation rates: the latter were usually below 0.35 mm. per minute in hypertrophic, above 0.35 mm. in atrophic arthritis (Rourke and Ernstene method). Gray [251] found the sedimentation rate (Westergren method) over 20 mm. per hour in only 2 per cent, 10 mm. or below in 85 per cent. Essentially similar rates were noted by others.[29, 34]

No relation between anemia and gastric acidity was found by Collins [268]; only one of 11 cases had reduced gastric acids. Of 35 cases, achlorhydria was found by Hartung and Steinbrocker [272] in 26 per cent, hypochlorhydria in 3 per cent (subacidity was 17 per cent more frequent in atrophic arthritis).

Values for total blood protein, globulin, albumin and plasma fibrinogen were normal in Davis' [29] cases of hypertrophic arthritis (generally abnormal in atrophic arthritis). Alterations in blood proteins were found by Aldred-Brown and Munro [257] when patients with hypertrophic arthritis (group 1) were compared to healthy young normals (group 2), but these differences tended to disappear when they were compared to non-rheumatic persons of less favorable economic status (group 3). The average values (gm. per 100 c.c. of plasma) were as follows. In groups 1, 2 and 3, respectively: albumin 3.91, 4.51, 4.09; globulin 2.32, 1.69, 2.13; fibrinogen 0.34, 0.16, 0.22; total protein 6.35, 6.37, 6.35. Thus plasma protein was low in hypertrophic, but not so low as in atrophic, arthritis.

Hartung and his associates [258, 259] found a tendency towards an elevated plasma cholesterol and a lowered serum calcium. Of 59 cases, 62 per cent had high, 3 per cent low, and 35 per cent normal, values for cholesterol (160 to 230 mg.). The mean total cholesterol was 235.4 ± 45 mg. Values for the mean and standard deviation of serum calcium were 9.986 ± 0.616 mg. per 100 c.c. (normal 10.241 ± 0.647 mg.). Race [260] noted a slight but definite tendency towards lower values for serum calcium in atrophic than in hypertrophic arthritis. Serum magnesium was essentially normal in hypertrophic and atrophic arthritis (a little lower in the latter). Blood groups were as in normals. There was no characteristic deviation in urinary acidity.

Etiology and Pathogenesis. Various writers have blamed each of the following factors as the sole cause of the disease: heredity, constitution, the degenerative processes of age, chronic trauma, circulatory disturbances, some specific metabolic fault, an endocrine disturbance, infection. Others believe that not one factor, but a combination of factors is responsible—particularly age plus chronic trauma. Still others believe there is one specific cause, as yet unknown, and that those mentioned are merely predisposing, precipitating, or accelerating factors of secondary importance.

Factor of Heredity and Constitution. Heredity is commonly blamed because patients state the disease " runs in the family." [103] Its incidence, however, is so general that practically all one's ancestors over 50 years of age had it. Others blame heredity not for the disease's general incidence as much as for its premature appearance. " Some patients inherit better cartilage than others. The poorer the inheritance and the greater the endogenous

and exogenous trauma, the earlier will hypertrophic arthritis develop" (Bauer and Bennett [29]). Pribram and Fahlstrom [261] are current sponsors of the idea of a constitutional tendency of brachymorphics for the disease, but many of Pemberton's [253] patients were slender.

Factor of Tissue Degeneration (Tissue Age). One's calendar and histologic ages are of course not identical. Furthermore, because of differences in the histologic "ages" of various organs, one's mental (cerebral) and general physical ages may be quite different. The majority believe that the histologic age of cartilage (age being the sum total of all traumatic and toxic insults of life) is the chief determinant of the disease. Hypertrophic arthritis represents a localized, premature senile change which may occur in clerks as well as bricklayers, from mental as well as physical overstrain (Howitt [263]).

Factor of Trauma. To some, "age" is but the sustained opportunity for mild long-continued articular trauma as a result of posture, obesity, occupation or recreation. They regard the disease as the result of such chronic trauma, or that from intra-articular or juxta-articular fractures with faulty alignment, unreduced dislocations, foreign bodies or other orthopedic disabilities.[13, 279, 283] Doub and Jones [12] related the disease to chronic but not to acute trauma since single severe trauma (juxta-articular fractures) seemed to play no rôle in the production of hypertrophic arthritis.

Factor of Circulatory Alterations. Circulatory deficiencies (arteriosclerotic, inflammatory, or vasospastic) leading to excess articular catabolism have been held responsible. However, no evidence is at hand that the nutrition of a person's osteo-arthritic joints is more deficient than that of his unaffected joints, or that there is more arteriosclerosis of nutrient vessels of the former than of the latter.[103]

Factor of Altered Metabolism. In contrast to the idea of a nonspecific metabolic defect from poor articular circulation is the theory that some more or less specific metabolic derangement is responsible, a disturbance in utilization of sugar, of calcium, of sulphur. A defect of the last type is now a popular notion, and some believe that hypertrophic as well as atrophic arthritis is due to a deficiency of sulphur in the body, particularly in cartilage.[255, 284-286, 288, 289] The majority have made no attempt whatever to differentiate the types of arthritis in which they found reduced cystine in nails or which improved on sulphur—merely labelling them "arthritis" or "chronic arthritis." Wheeldon [255] noted that the average cystine content of nails was a little lower and rose higher after treatment in hypertrophic, than in atrophic, arthritis. Senturia [287] found no abnormal urinary excretion of sulphur in either type.

(It is impossible for a critical reader to form any conclusions when even the types of arthritis treated are not differentiated.—Ed.)

Some are still keeping alive the notion that the disease is related to a purine disturbance since "the blood uric acid is always increased." [295] (This has long since been disproved by numerous careful investigators.—Ed.)

Todd [290] "slightly" incriminated "the hepatic factor," and Miller [291] noted hepatic dysfunction (an altered levulose tolerance) as often in hypertrophic as in atrophic arthritis (in about a third of each group).

No causal relationship between hypertrophic arthritis and any metabolic disturbance associated with diet was found by Bauer [294] or by Hall and Myers.[292] According to Langstroth [316] the relationship of the disease to diet is a paradoxical one; although there is no evidence that its victims have eaten less "protective foods" than others, the administration of such foods is of value.

Factor of Endocrine Disturbances. Although the disease frequently becomes symptomatic near the menopause, no definite connection between it and endocrine glands has been proved. Since hypertrophic arthritis occurred in only 1.7 per cent of 414 cases of hyperthyroidism, no relationship between these two diseases was apparent to Monroe.[296] However, of 98 patients with myxedema, 33 per cent had hypertrophic arthritis, "an intimate and important association." Their average age was 51 years, but myxedema and not just age was considered the major factor.

Of Haden's [29] 50 cases of hypertrophic arthritis, a "low" metabolic rate was found in 84 per cent, an accelerating factor considered important.

(Many others, e.g. Race,[260] considered metabolic rates to be normal.—Ed.)

Factor of Infection. The factor of infection seems unimportant to the majority.[29] There is little or no direct evidence of infection, and various immunologic reactions used as evidence of the infectious nature of atrophic arthritis are usually absent in hypertrophic arthritis. Blood cultures by Gray [251] in 79 cases were all negative for streptococci. Agglutinins to hemolytic streptococci were not found by Dawson.[103] They were rarely found by Gray, Bernhard and Gowen [269] in significant amounts (1 : 160 or higher): they were present in low titer (0 to 80) in 83 per cent of cases, in a titer of 160 to 320 in 17 per cent; none in higher dilutions. In only three of Blair and Hallman's [206] 16 cases were agglutinins to Cecil's "typical" streptococcus found in dilutions greater than 1 : 160. Antistreptolysins in abnormal amounts (over 100 units) were found in only two of 13 cases of "chronic arthritis other than rheumatoid." Skin reactions to hemolytic and green streptococci were absent in four, present in six cases of Wainwright.[278] One patient reacted to two strains, two patients to three strains and three to five strains or more.

(No interpretation was offered.—Ed.)

Some believe, however, that infection plays a contributory rôle. Pemberton [253] reported two cases: one patient responded "immediately" to the removal of infected teeth, suggesting that infection played a rôle, and the other to rest, diet and improved intestinal function, suggesting that age alone was not responsible. The difference between a painful joint with hypertrophic arthritis and a painless one roentgenographically even more hyper-

trophic, is generally thought to be the factor of trauma, but Sherwood [303] agreed with Key (1933) that low grade infection may produce pain in joints which would otherwise be symptomless. Bauer [29] ascribed the variable presence of pain to changing pathology. When marginal osteoid tissue proliferation is occurring, periosteum may become elevated and pain results. When this osteoid proliferation ceases and the tissue becomes calcified pain may stop.

Treatment. Perhaps the most important part of treatment is to explain to the patient the differences in the nature, particularly in the prognosis, of the disease he actually has from that which he thinks he has, and to assure him that hypertrophic arthritis (unlike atrophic, "deforming arthritis" which he fears) is not essentially an ankylosing, severely-crippling, progressive disease. This done, many patients neither ask nor accept other treatment but bear their difficulty philosophically without the "nuisance of treatment" (Hench [106]).

Rest and Reduction of Trauma. Many patients are deliberately overexercising under the erroneous impression that "unless the joints are kept active they will stiffen." With the onset of symptoms of hypertrophic arthritis patients often go out of their way to activate the joints, "to keep limber," grimly determined to keep going. This only irritates the process and is harmful and unnecessary, as ankylosis is not characteristic of the disease. Generous rest and the reduction of trauma are highly desirable, although not to the extent that the patient feels himself a crippled invalid.[13, 106, 253, 283] Extra hours of rest at night and in the daytime, reduction of obesity, and the use of a cane, corset or roller bandage, will minimize trauma and permit a patient to be comfortable when he is active.

Diet. Reduction of tissue edema and relief by means of the mild, dehydrating effect of a low-carbohydrate, low-calorie diet were noted by Scull and Pemberton [314, 315] in hypertrophic, as well as in atrophic, arthritis. Others found no special dietary indications for the disease except for the reduction of obesity.[292, 294]

Removal of Foci. This has seemed useless in the majority of cases, though it may be indicated in particular instances.[253, 304]

Vaccines. Vaccines are generally not prescribed. Sherwood [303, 309] treated 260 patients with various vaccines with results which were considered as good as those obtained in atrophic arthritis.

(He stated that neither the severity of symptoms nor the type of arthritis influenced the results from vaccine. This experience is at variance with that of the majority and makes one doubt the value of the vaccine, particularly when a definite, if smaller [33 per cent], number of controls improved on saline injections.—Ed.)

Young,[383] an associate of Crowe, used the latter's vaccine "successfully" in treatment of 100 cases of "osteo-arthritis." Contrary to what is customary, their plan is one of progressively *smaller,* not larger, doses of vaccine. McCarty [325] also considered (intravenous) vaccines helpful for pain, but less so than in atrophic arthritis.

Sulphur. Relief from injections of sulphur was reported in hypertrophic as well as in atrophic arthritis.[255] Good results ensued "in every case" (five) in one series,[285, 286] in 50 per cent of another series (26 cases),[284] but in only three of eight cases in a third group.[324]

Gold Injections. Such injections were used in the hypertrophic type also. In a series of 17 cases, Pemberton [323] (Liverpool) noted much improvement in 24 per cent, improvement in 13 per cent. For intractable osteo-arthritis Slot [42] combined the use of gold with epidural injections of procaine. Forestier [41] found gold of no value in osteo-arthritis.

Iontophoresis with Vasodilating Drugs. Of 25 patients treated with histamine by Kling [17] 60 per cent improved. Of 29 patients treated with mecholyl by Abel [326] 90 per cent had relief of pain; Kovacs,[327] however, noted no relief with mecholyl.

Miscellaneous. Thyroid extract was used by some.[103] Relief of pain was obtained by Forestier [384] with local injections of lipiodol (perineural, peri-articular). Ten of 18 patients improved while on large doses of vitamin D (concentrated viosterol) (Dreyer and Reed [331]).

Physical Therapy. This, of course, is extensively advocated. Underwater therapy is especially valuable for elderly patients with hypertrophic arthritis.[358] Some advocated short-wave therapy.[79, 354, 356] Diathermy was particularly approved by Kovacs.[327] Roentgen therapy was used by Garland [40] in seven cases of hypertrophic spondylitis: only one patient became symptom-free but four "improved." Fever therapy is cautiously approved by some,[47, 73] considered of no value by others,[51, 74] Tenney and Snow noted improvement in only four of 10 cases.[385] Various other physicians have treated a total of 74 patients: only 4 per cent became symptom-free, about 50 per cent noted some relief.[48]

Orthopedic Treatment. Considerable relief may result from manipulation in selected cases, such as osteo-arthritis of the cervical or lumbar spine, or hip.[10, 318, 334, 377, 379] Synovectomy may help some patients greatly.[334, 373] Bone puncture (Mackenzie, 1931–1932) relieved a few, failed in other cases.[99] Cheilotomy to remove femoral osteophytes has not been very successful and is inferior to hip joint resection.[334] Because bony union is difficult to obtain, arthrodesis is less useful than reconstruction of hip joints.

Backache and Sciatica

Backache and sciatica are not, of course, diseases per se but symptoms of many diseases. The anatomic physiology of the spine and its adjacent tissues is so complicated that experienced orthopedists at times have great difficulty in determining the cause of backache or sciatica. The physician without at least some orthopedic training is even more confused. He is apt to examine the spine for rather gross stiffness, look for spurs in roentgenograms and, if there is a poker spine, the diagnosis becomes "ankylosing spondylitis" (or an equivalent term). If there are spurs the diagnosis

becomes "hypertrophic spondylitis." If neither is present the diagnosis becomes simply "backache." Going a little farther, he may offer a favorite explanation: "backache due to poor posture," from "uterine displacement," from "strain" or "fatigue."

The literature reviewed contained about 50 articles on, and about as many classifications of, backache. Backache can be briefly classified as being: from (1) primary neurologic conditions; (2) genito-urinary disease; (3) gynecologic disturbances ("post-pregnancy backache," etc.); (4) metastatic malignancy; and (5) "orthopedic conditions." Commoner orthopedic conditions which produce backache are postural or occupational strain of muscles and ligaments, infections of ligaments, muscles and their fibrous tissue (toxic or infectious "myofasciitis" or "paravertebral fibrositis"), developmental anomalies of the fifth lumbar and first sacral region, disturbances of the intervertebral disks, and (traumatic, infectious or degenerative) arthritis of the vertebral bodies or articular facets, or both.

The lower back is a common site of symptoms in the malingerer, be it the industrial worker seeking compensation or the tired housewife seeking sympathy. Points useful in detecting malingering were listed by Stuck.[386] To be determined are: (1) an estimate of the patient's sincerity of purpose from his general demeanor; (2) whether his general body build and posture (tall, thin), or his occupation are such as to make him liable to injury; (3) a reasonable consistency between the severity of the injury and that of symptoms. (In general there is a correlation between the two, although there are exceptions and trivial injuries may induce severe backache, and only mild damage may result from a violent accident); (4) the relationship between the time of injury and the onset of symptoms (as a rule symptoms appear within a few hours); (5) presence or absence of previous backache; (6) in the presence of organic disease examination will generally reveal muscle spasm, sometimes scoliosis, it being difficult if not impossible for a malingerer to feign muscle spasm or scoliosis except momentarily; (7) with organic disease, tender spots remain rather consistently localized during the first and subsequent examinations, malingerers rarely recalling the sites of previous "tenderness" carefully enough to avoid detection, and (8) the newer technic of making roentgenograms (Ghormley and Kirklin, 1934) will reveal disease of facets as well as of vertebral bodies.

The technic and significance of various manipulative methods of examining the back to localize disease of the spine were reviewed by several.[386-396] Some considered the physical examination much more valuable in certain cases than roentgenograms because the latter may reveal changes (spurs, anomalies) which may or may not be related to the presenting symptoms. Without careful investigation symptoms must not be too readily blamed on the hypertrophic lipping so commonly seen in laborers and in the obese over 40 years, and in others over 50 years of age.

Comments on Differentiation. Figures on the percentage of cases of

backache from arthritis are not always reliable as they are often colored by a physician's special knowledge or lack of it. If in a given case pelvic disease is present, a gynecologist may blame the backache thereon without seeking a further explanation; if pelvic disease is absent he may rightly or wrongly dismiss the case as of "rheumatic origin." The practitioner may blame poor posture in a case when roentgenograms of the spine are apparently "negative." (The word "apparently" is used advisedly as, too often, roentgenographic examination is limited to an antero-posterior view of the spine, and lateral and oblique ["three-quarter"] views are not taken.—Ed.) Of 63 cases of backache seen by Shafiroff and Sava [397] 70 per cent were from "arthritis," of which 50 per cent were ascribed to "traumatic arthritis of facets," 39 per cent to "lumbosacral and sacro-iliac osteoarthritis," and 11 per cent to "generalized arthritis." They concluded that in backache from pelvic disease the pain was likely to be diffusely spread over the back and referred anteriorly to the legs from pressure on iliohypogastric, ilioinguinal, and femoral nerves, but that in backache from osseous disease, pain is more localized to the affected area and is projected generally along the posterior portion of the leg from pressure on sacral nerves.

(The data given are inadequate for the reader to accept fully the diagnoses and differentiation.—Ed.)

In differentiation Gotten [398] characterized the pain of lumbosacral myositis as being usually aggravated by cold or damp and partially relieved by exercise, while that of arthritis is aggravated by exercise. Of the common types of backache—traumatic, infectious, and static or attitudinal—the last constitutes 90 per cent, according to Davidson and Horowitz,[399] and frequently leads to microtraumatic arthritis. Certain differences were noted by Magnuson.[393] Pain which is worse in the morning on rising, but disappears after brief activity is frequently due to "periarthritis" of paravertebral ligaments and muscles, a condition which often causes night-backache, because of which a patient awakes to find a more comfortable position. A backache appearing in the afternoon or evening is more frequently due to fatigue, poor posture or arthritis.

(As generalizations these statements are fairly sound, but it must be remembered that many cases of spondylitis are associated with paravertebral fibromyositis, symptoms of which may dominate at times, in which case the patient may feel worse on rising, better after some exercise.—Ed.)

The "Newer Anatomy" of the Spine. Until recently studies on spondylitis dealt almost exclusively with diseases of the vertebral bodies and adjacent ligaments. In atrophic spondylitis (spondylitis ankylopoietica) the chief pathologic finding was regarded as inflammation and calcification of paravertebral ligaments, the vertebral bodies not being affected early except by atrophy. In hypertrophic spondylitis (spondylitis osteoarthritica) lipping of vertebral bodies was evident. So, too, in suspected traumatic spondylitis roentgenographic evidences of trauma were sought in

vertebral bodies; if these appeared normal pain was ascribed to traumatized muscles and ligaments. However, since the work of Schmorl (1927 et seq.), Schmorl and Junghanns (1932), Beadle (1931), Ghormley (1931 et seq.), Keyes and Compere (1932–1933) and others, major interest has been transferred to the anatomy and pathology of the intervertebral disks and "paravertebral joints" or lateral "facets." Now it appears that a great number of cases of backache, (secondary) spondylitis and sciatica are due to diseases primarily not in the larger, more obvious, vertebral bodies but in the smaller structures—disks and facets. Thus current writers have given much space to discussions on the "newer anatomy and pathology" of these tissues. Since the work to which they refer in truth constituted "a new chapter on vertebral pathology," it seems well to review it here in some detail. (Since current writers freely referred to the reports of Schmorl and the others just mentioned, it was at times difficult to know when they were quoting and when they were presenting original observations. The following is a summary of data reviewed by them.—Ed.)

One is likely to consider the spine as consisting of 24 vertebral bodies with their 23 intervertebral joints. As a matter of fact, according to Rechtman [395] there are 134 joints in the spine between the skull and the sacrum, each vertebra having approximately 10 synovial-lined cavities. Furthermore, the 23 intervertebral "joints"—the spaces between the vertebral bodies—are not true joints at all, since they possess no synovial membrane but are made up of fibrocartilage—the intervertebral disks. These disks are composed of three main parts: the cartilage end-plates, the annulus fibrosus, and the nucleus pulposus. Each disk is bounded above and below by a vertebral body, the peripheral bony edges of which are slightly thickened anteriorly and laterally (but not posteriorly) to form the "epiphyseal ring."

The cartilage plates are thin layers of hyaline cartilage which form the top and bottom of the intervertebral disk and which fuse anteriorly and laterally with the bony edges or epiphyseal ring of the vertebrae to form the "rim ledge." The cartilage plates in turn enclose the "annulus lamellosus" or "annulus fibrosus," a dense fibrocartilaginous envelope composed of concentric folds of fibrous tissue. These folds form a strong elastic container for the nucleus pulposus, except toward the posterior edge of the disk (toward the spinal canal) where the fibers of the annulus are fewer and thinner.

The "heart" or "central lens" of the intervertebral disk is the nucleus pulposus, a fibrogelatinous incompressible mass of tissue, partly cellular, partly fluid (88 per cent water at birth). Thus it is subject to the usual laws of fluids—it is under tension, and is capable of expansion but not of compression. The pressure of the nucleus pulposus after cutting away the annulus fibrosus is 1.8 mm. of mercury. The pressure required to reduce its expansion is 32.2 pounds.[400] The position of the nucleus pulposus within the annulus fibrosus varies in different spinal segments; it is always rather more posterior than central but is farther forward in the upper thoracic region. The nucleus acts as a shock-absorber and diminishes the effect of

stress and strain on the spine, and at the same time it is the medium of transmitting pressure from one vertebra to the next. It is confined to its normal shape and position by the strong surrounding bands of the annulus fibrosus and it is on the integrity of the latter and of the cartilage plates that the normal function of the nucleus depends.

The simplest way to understand the intervertebral disk is perhaps to regard it as a rudimentary (but not a true) joint; the cartilage plates are comparable to articular cartilage, the annulus fibrosus to fibrous articular capsule, and the nucleus pulposus to a joint cavity (Malcolmson[401]). The disks have the function, then, of being buffers and hydrostatic ball-bearings (Hadley[402]), and it is largely on the integrity of these disks that the normal function of the spine depends (Carpenter[403]). The disks in embryonic life have blood vessels,[400] but the adult disk is thought to have no blood vessels. It gets its nutrition by diffusion of lymph through minute perforations in the bony surface of the spongy vertebral bodies. The disk has no nerves either, and since it has no nerves, the disk when diseased is per se painless. Pain is produced only when secondary changes occur in vertebral bodies and facets (Hart[404]). Since the disks have no blood supply they cannot become infected directly through the blood stream; however, they may be infected via lymph channels, and suppuration in the region of a disk may attack and destroy it.[405, 406]

The only true joints of the spine are those which connect the superior and inferior (lateral) spinous processes. In the literature they are variously named "lateral intervertebral articulations" or joints,[407] "intervertebral synovial joints,"[408] "apophyseal articulations" or "posterior articulations of the spine,"[402] and "articular facets."[409] They are true diarthrodial joints and possess joint cavities. Hyaline cartilage covers their surfaces, and they possess synovial membranes, articular capsules and articular ligaments. Hence they are subject to the same injuries and diseases that affect joints elsewhere.

The function of these joints is to permit motion in the spine and to act as stabilizers, but not to carry weight, which in a position of good posture they do not carry. Each joint permits only a fraction of an inch of motion, yet many of them together permit an appreciable amount. Leverage determines to a large degree the amount of force transmitted to the capsules of these joints, it being progressively less toward the head and progressively greater toward the sacrum, the greatest force being at the lumbosacral joint because the lateral intervertebral articulations are more or less in the sagittal plane, except at the lumbosacral joint where they are more obliquely situated. Therefore, at the lumbosacral joint an antero-posterior roentgenographic view does not show the joints in profile as it does in higher lumbar joints.

Ligaments and muscles usually prevent damage to the lateral intervertebral joints, even to those of the lumbosacral region, where the fifth lumbar body is normally inclined upon the first sacral at an angle of 40°. Here,

forward slipping is prevented by the inferior articular process of the fifth lumbar vertebra and by surrounding ligaments. The spinal nerves escape on each side by way of the spinal foramina, which vary in size as do the nerves. Unfortunately the smallest of the lumbar foramina is the fifth, through which the largest nerve trunk passes, and this has much to do with the great frequency of low-back pain involving the fifth nerve.[407]

Pathologic Conditions Affecting the Intervertebral Disk; Results Thereof. The parts of the intervertebral disks are so interdependent that disease of one part leads to disease of others. *Cartilage plates* may be affected variously: 1. Congenital defects, fissures or cracks, may weaken them and lead to prolapse of the nucleus pulposus. 2. Acute trauma may injure them and cause prompt escape of the nucleus pulposus. Roentgenograms will be negative for several months until thinning of the disks becomes apparent, until the nucleus, if it prolapsed into the spongiosum, becomes calcified, or until secondary osteo-arthritic changes become obvious. 3. Chronic trauma, particularly in the third and fourth decades of life, may injure the plate.[403] Fibrillation from wear and tear in hard workers or in the aged, or even continued every day trauma, will cause minute cracks in the plates, with resultant dehydration, lessened resilience, thinning and destruction of the disk, excessive wear and tear on the margins of vertebral bodies, and subsequent osteo-arthritis (Schmorl). However, since Schmorl often found better preserved disks in the aged than in people of sedentary occupation, he concluded that the ordinary trauma of daily work plus individual constitutional factors, which vary greatly in different persons, plays a greater rôle than disease in producing degenerative changes in the disks. 4. Primary disease of cartilage plates is unknown or rare, but they may be secondarily invaded by diseases of the vertebral bodies, for example, tuberculosis and osteomyelitis.

The *nucleus pulposus* may be affected in several ways: 1. Retropulsion, or antepulsion, of the nucleus within the disk [403] or prolapse of a nucleus into the spongiosum of an adjacent vertebral body may occur, chiefly from injuries producing tears in the annulus fibrosus, in cartilage plates, or both. Retropulsion of a nucleus into the spinal canal may occur and produce pain (with or without neurologic findings) and even paraplegia (Malcolmson,[401] Carpenter,[403] Mixter and Ayer [410]). Schmorl found some degrees of prolapse of nuclei in 38 per cent of 5,000 routine necropsies. If only a small portion of a nucleus is extruded, function of a disk may not be seriously impaired for a time, but dehydration and diminished function of a disk may later appear at an earlier age than otherwise. 2. Lateral shift of a nucleus to the convexity of the curve may occur, as in cases of sclerosis.[401] 3. Calcification of the nucleus may result from unknown causes, presumably from disturbances in calcium metabolism, trauma, senility, infection and so forth.[403] Such deposits increase with age. They may appear in the nucleus or in the annulus; Ratheke (1932, cited by Joplin) found 6.5 per cent of

them in the nucleus, 71 per cent in the annulus. They appear in roentgenograms as branched shadows with several processes, projecting outward. They are generally in the central portion of the disk, but also in the periphery of the fibrous ring. 4. Dehydration occurs with advanced age. The water content of the nucleus at birth is 88 per cent, at 18 years 80 per cent, at 77 years 69 per cent. Thus progressive dehydration begins in the third and fourth decade [400] and accompanies senility, but stress and strain hasten its development and it can be rapidly brought about by leakage of the nucleus from the several causes noted.[401] 5. Infiltration of the nucleus by other tissue may occur, by bone or blood vessels, and especially by fibrous tissue replacement of old age or during health after trauma. 6. " Expansion " of nuclei sometimes occurs from release of pressure when adjacent vertebral bodies become softened from osteochondritis, osteitis fibrosa, senile osteoporosis, or neoplastic invasion. As a result of nuclear expansion, the disks appear spherical in roentgenograms, the vertebral bodies appear biconcave.[403] In extreme cases adjacent intervertebral disks may almost touch [400]; roentgenograms then show thick disks and thin biconcave vertebral bodies. Enlargement of disks in such cases was believed by Schmorl (1930) to be due to " expansion," by Moffett (1933) to result from compensatory hypertrophy.

Disturbances of *intervertebral disks* include: (1) congenital absence of a disk,[401] (2) drying of tissue of the disk, (3) occurrence of fissures primarily in the disk, and (4) increased moisture in tissues of the disk, inducing gross fissure formation and ultimately destroying the disk. Infection of the disk via the blood stream presumably does not occur as the disk has no blood supply.[405] (This is doubted by Böhmig.[411]) However, suppuration adjacent to a disk may attack and destroy it. Changes in the disk become so frequent with advancing age that, after the middle of the sixth decade, it is almost impossible to find a spine in which all disks are normal.[405] Degeneration in the disk is characterized by a grinding up and drying out process with deposition of yellowish or brownish pigment of unknown composition. Large cavities are produced in the interior, but the outer periphery of the annulus fibrosus may remain intact.[400]

The eventual thinning and tendency to partial or complete destruction of the disks plays a large part in the production of several clinical syndromes: (1) hypertrophic (osteo-) arthritis of vertebral bodies and of facets, (2) radiculitis at various levels, (3) sciatica, (4) low back pain with or without sciatica, (5) occasional symptoms simulating those of cord tumor.

When Keyes and Compere (1933) punctured the annulus fibrosus of animals and allowed nuclear material to escape with prolapse of the nucleus into adjacent vertebral bodies, there ensued destruction of the disk, lipping of vertebrae, and osteo-arthritis. The same sequence of events occurs in man. Whenever thinning and destruction of disks occur, the vertebral bodies rub together, causing sclerosis, osteo-arthritis and lipping.[401] As

noted, since disks contain no nerves, disease of disks is not painful per se until the development of vertebral or facet changes.[403] Some regard the vertebral osteophytes as evidence, not of arthritis, but of an attempt at stabilization; hence they prefer "spondylosis" to "spondylitis" (Beadle, 1931).

It is important from the medicolegal standpoint to realize that the radiologic diagnosis of disease of disks may have to be delayed several months after injury until secondary changes occur. Roentgenograms may not at once reveal all the damage from acute trauma; nuclear prolapse is not at once associated with visible roentgenographic changes. Conclusions must be drawn from the width of the intervertebral space and the condition of the borders of the adjacent vertebral bodies. Weakness of cartilage plates may be evidenced radiologically by the pressure of smooth excavations (umbilication of disk material) into vertebral bodies (Malcolmson [401]). When nuclear prolapse occurs, the first change is a fibrous tissue reaction. About a month later this is replaced by a rim of cartilage which becomes surrounded by a wall of sclerosed bone. The space becomes hollowed, and later (three or four months after injury), deposits of calcium in vertebral bodies become visible in roentgenograms. These Schmorl's knots [401] or nodules [400] were previously thought to be enchondromas of the intervertebral disk (Mixter and Ayer [410]).

Pathologic Conditions Affecting the Facets; Results Thereof. The lateral intervertebral joints or "facets" may be affected: (1) directly as the result of trauma, degeneration or disease, or (2) secondarily in connection with disease of the intervertebral disks and vertebral bodies. Occasionally a sudden forcible motion of the spine is too great or too quick for muscles to protect the capsule of the facet adequately. The capsule is strained, some of its fibers are ruptured, and local pain and muscle spasm are found, but roentgenograms do not show the synovitis of these joints or the swelling of its capsular ligaments.[407]

Rupture of a nucleus pulposus and narrowing of a disk will cause subluxation of the adjacent facet articulations. If enough fluid escapes so that the nucleus is destroyed, the disk thins and the vertebrae begin to settle, the axis of motion is shifted posteriorly to the articular facets, and the weight of the body is transferred to the lateral or anterior part of the vertebral bodies. Partial subluxation of articular facets and a diminution in the size of intervertebral foramina ensues (this is nicely shown in photographs by Hadley,[402] and in diagrams by Hart [404]). Local and referred pains are produced by tension on capsular ligaments, encroachment on the size of the lumen of the foramina, and impingement of the ends of the articular processes on the pedicle above and the lamina below (both of which are covered by periosteum). The over-riding and abnormal contact of the surfaces of the facets produce degeneration of cartilage, marginal hyperplasia and

exostoses which still further decrease the diameter of the foramen and lead to radiculitis.[402, 406]

Production of Low Backache and Secondary Sciatica. When the series of events just noted occurs at the lumbosacral joint it is particularly productive of symptoms, commonly low backache and sciatica. The sciatic nerve is derived from the anterior divisions of the fourth and fifth lumbar and the first, second and third sacral nerves. The fifth lumbar nerve is, as has been said, the largest one but must traverse the smallest foramen. It lies between the lumbosacral intervertebral disk and the lumbosacral articular facets and may become involved in inflammation, either of the disk or facets. Sciatic radiculitis frequently results.

That the intervertebral foramina are " the crossroads of neuralgia " was borne out by the experience of Putti [412] who noted " vertebral sciatica " in 231 of 345 cases of lumbar arthritis. According to Ghormley (1933) sciatica is more frequently caused by pressure on nerves or nerve sheaths at diseased facets than by disease of intervertebral disks.

Lumbosacral congenital anomalies, present in about 35 per cent of all persons [404] are frequent, some say the most frequent cause of sciatica or low back pain (O'Conner,[413] Bellerose [414]). The fifth lumbar vertebra is in the process of developmental transition. In Wagner's [415] cases defects here produced pain involving or including the third lumbar to the third sacral segment, but most particularly the fifth lumbar and the first and second sacral segments of the spinal cord.

In occasional cases sciatica was found by Ayres [406] and Mixter and Ayer [410] to be due to rupture of the intervertebral disk into the spinal canal. About 50 per cent of such ruptures implicate the fourth to fifth lumbar disks: 23 of their 34 cases, 42 of 81 collected cases. Usually fragments of both annulus and nucleus were present, hence " rupture of the disk " is a more correct term than " rupture of the nucleus." The herniated mass varied from 0.5 to 2 cm. in size. Trauma was the most frequent cause. Symptoms may not appear immediately thereafter. In lumbosacral herniation symptoms may be of sacro-iliac or low-back pain, of severe intermittent sciatica, or of caudal tumors. (Malcolmson [401] noted paraplegia in one case). Neurologic examination was sometimes negative. The protein content of spinal fluid was almost always increased (in 33 of 34 cases), even in spinal fluid from above the level of the hernia. Injections of lipiodol revealed partial subarachnoid block. Therefore, not even a tentative diagnosis of herniated disk should be made without finding increased protein in spinal fluid and a positive lipiodol test.

(Among a fairly large number of cases in which rupture of the disk into the spinal canal was proved at operation by neurosurgeons at The Mayo Clinic were several in which the protein content of the spinal fluid was normal. In only 20 per cent of the entire series was there roentgenographic evidence of thinning of intervertebral disks.—Ed.)

Of additional interest are the following representative articles: on low-back pain "commonly caused" by a tight iliotibial band [389, 416] and a description of the Ober method of treating the condition by sectioning the fascia lata; arguments for [417] and against [418] the idea that backache is frequently caused by sacro-iliac subluxation; backache from the urologic viewpoint [419, 420]; gynecologic conditions, such as displaced uterus or malfunctioning ovaries as a common [421, 422] or rare [397, 398] cause of backache; the diagnosis of destructive spinal lesions by "needle-biopsy" [423]; and on manipulation in low-back pain from trauma and poor posture (Cox,[424] Wright [417]). A partial translation of Cotugno's *De ischia de nervosa commentarius* (1764) was given by Viets [425] with interesting historical comments.

The Treatment of Low-Back Pain and Secondary Sciatica. This is most variable and depends on the cause. Hart [404] and Hadley [402] favored conservative treatment: physiologic rest (on a firm bed, with or without extension, strapping, jackets, braces) and hyperemia by various physical means. Roentgen therapy was distinctly helpful, Hadley stated. When conservative therapy failed, spine fusion or facetectomy was advised. Of 99 patients with "lumbosacral pathology" seen by Ayres,[406] 59 had thinned disks. The results of Hibb's fusion operation, followed by the use of a jacket or brace, were successful in 80 cases, patients being well two to 10 years after operation. Facetectomy was not necessary, and Ayres felt that if it were done with fusion the resultant mass of callus might involve the fifth lumbar nerve adversely.

Common Types of Spondylitis

Excluding spondylitis due to frank trauma and specific infection, Kreuscher [391] distinguished three types: hypertrophic spondylitis, atrophic spondylitis, "which generally goes on to ankylosis," and nonspecific "infectious spondylitis," which is "often relieved by removal of infected foci." (The distinctions are not clarified further.—Ed.) Some regard spondylitis rhizomelique, or the Marie-Strumpell type, and the von Bechterew type as different diseases. Spondylitis rhizomelique, spondylitis ankylopoietica, and the von Bechterew and Strumpell types are all regarded by Buckley [426] as the same disease, "ankylosing spondylitis," which, however, he considered distinct from, and not the spinal equivalent of, atrophic arthritis, because of the sharply-contrasting sex incidence and because, with ankylosing spondylitis, it is rare for more distal joints to be implicated. Even when peripheral joints are affected therewith, "such cases may be distinguished from rheumatoid arthritis by the order of invasion, the spine and large joints preceding those of the extremities."

(The editors consider that some of these distinctions are relatively unimportant, that the von Bechterew and Strumpell types are probably varieties of atrophic spondylitis, and that the two great common types of spondylitis are atrophic spondylitis, the equivalent of atrophic arthritis elsewhere, and hypertrophic spondylitis, the spinal representative of hypertrophic arthritis as seen in peripheral joints.—Ed.)

Atrophic Spondylitis. The relative incidence of atrophic spondylitis to atrophic arthritis was 1 : 13 in one series.[103]

Symptoms. The usual symptoms were reviewed by several, for example by Buckley [426, 427] who also summarized studies on the nervous manifestations of "vertebral rheumatism." Root pains and reflex changes may occur in both types of spondylitis. In hypertrophic spondylitis, nerve symptoms are due to formation of exostoses, not from inflammatory exudates: in atrophic spondylitis, however, they are rarely due to compression from exostoses or ossified ligaments but to inflammatory lesions of the epidural spaces or meninges. Nerve pains are more frequent in the pre-ankylosing stage than when the spine is fixed, but girdle pains in the lower intercostal regions may be present after ankylosis has begun, probably from new bone deposits on the sides of the vertebral bodies. In cases of brachial neuritis and minor nervous symptoms in arms, profile roentgenograms may reveal atrophy of the lower cervical vertebrae, with or without spondylitis, a point for further investigation.[427]

Pathology. This was described again: bony ankylosis of vertebral bodies, not from osteophytes, but from calcification of vertebral ligaments, circumferential ossification of intervertebral disks, rarefaction and softening of vertebral bodies, and destruction and ankylosis of sacro-iliac joints.[426] (Also ankylosis of lateral intervertebral joints [facets], and costovertebral joints.—Ed.)

Roentgenograms. These reveal a variable state, ossification being early in some cases, late in others. Several noted early involvement of sacro-iliac joints (Buckley,[426] Dawson [103]), and Scott [428] regarded it as of particular significance. Of his 110 cases of "spondylitis adolescens," all showed bilateral infections of sacro-iliac joints with ankylosis. According to him, sacro-iliac infection is long symptomless and generally starts several years prior to symptoms in the sacro-iliac joints themselves or in the back elsewhere. Later, wandering pains about the shoulders, arms, ribs and legs may appear: in all such cases roentgenograms of the (painless) sacro-iliac joints should be taken to detect the early stage of spondylitis—the sacro-iliac infection. According to Scott, spinal symptoms do not begin until ankylosis of sacro-iliac joints has begun.

Laboratory Data. The plasma fibrinogen and total protein were higher in 12 cases of atrophic spondylitis than in cases of atrophic or hypertrophic arthritis (in other joints) seen by Aldred-Brown and Monroe.[257] Agglutinins to hemolytic streptococci are present in much lower amounts than in atrophic arthritis elsewhere (Dawson [103]).

Etiology and Pathogenesis. The cause of the disease is believed by the majority to be the same as that of atrophic arthritis (elsewhere). Buckley [426] was in sympathy with Leri's idea that atrophic spondylitis is not a disease of joints primarily, but of bone, "an infectious or toxic osteopathy," and that the bacterium might be found in spongiosa. In seven of 13 cases he noted increases in phosphoric esterase (phosphatase) of the blood, but he

considered this insufficient proof of a primary bone disease. Scott [428] believed the primary cause of spondylitis to be the early sacro-iliac infection, which "in spite of meager evidence" may commonly be of tuberculous nature. Because it is so important to prevent the spread of the infection to vertebrae, Scott stressed the necessity of discovering the sacro-iliac infection early, before spinal or even sacro-iliac symptoms have arisen, by making roentgenograms of the sacro-iliac joints in all cases with "wandering pains" in the back.

(Our experiences confirm the observation of Scott that sacro-iliac changes are often present long before other roentgenographic alterations. Buckley, however, did not note sacro-iliac changes in every case. Further investigation is necessary before one can accept the pathogenesis of the disease as outlined by Scott.—Ed.)

Treatment. Scott further noted that to remove the sacro-iliac focus, "trephining and curetting of the sacro-iliac joints before the onset of ankylosis are being tried," also, irradiation of the spine and sacro-iliac joints by low doses of roentgen-rays of medium wave length. No results were given. Conventional treatment was advocated by most: removal of foci, physiotherapy, belts, corsets or braces, and manipulation in selected cases.[390, 398] Mecholyl iontophoresis was of no value (Abel [326]). The use of vaccine gave no relief (Sherwood [309]), though it made supervision of patients easier. Wilson [355, 356] noted relief with short wave therapy.

Hypertrophic Spondylitis. The synonyms are: spondylitis osteoarthritica; spondylosis; spondylarthritis. To illustrate the new anatomic distinctions, Hawley [409] used the term "spondylitis" referring to changes in vertebral bodies, and "arthritis of the spine" referring to "true spinal arthritis"—that of facet articulations. Thus also Shore,[408, 429] in his studies on osteo-arthritis of the spine, preferred the term "polyspondylitis marginalis osteophytica" for (hypertrophic) osteo-arthritis of the vertebral bodies, anatomically a different disease from "osteo-arthritis of the dorsal intervertebral joints, the small synovial joints of the vertebral column."

Symptoms. Current reports stress the nervous symptoms that may arise. Rosenberger [430] attributed some cases of Horner's syndrome to (hypertrophic?) arthritis of the last cervical and first thoracic vertebrae. On certain movements of the head some patients noted neuralgic pains referable to the precordium or scapula, or spasm of the trapezius muscle. When symptoms arise from involvement of the upper three cervical vertebrae, occipital or suboccipital headache and pains in the neck may arise.[382] Keefer [382] considered sensory changes common, but according to Rosenberger they are uncommon, as the involved nerves carry no sensory fibers to the skin. Each of three sisters, aged 67, 51 and 45 years, presented to Zabriskie, Hare and Masselink [431] a curiously similar syndrome of hypertrophic arthritis of the last four cervical (in the oldest patient, also of the thoracic and lumbar) vertebrae, subjective numbness and tingling of finger tips and atrophy of the thenar muscles of both hands. The atrophy was

believed due to direct pressure on spinal nerve roots at some point of their exit from the spinal canal. The onset of symptoms in these cases was between 44 and 49 years of age. No parallel syndrome was found in the literature. However, atrophy of thenar and hypothenar eminences was listed in Buckley's [427] review of nerve manifestations of vertebral rheumatism; also noted were atrophy of other small muscles of the hand, atrophy of the Aran-Duchenne type, root atrophy of muscles (especially of leg and thigh), paresthesias, numbness and slight anesthesia, and sometimes muscle fibrillation and reflex changes. It was noted that osteophytes are sometimes seen at the vertebral level of root pain but on the side opposite the distribution of pain, indicating that it is not the formed osteophytes that produce pressure on nerve roots, but those in course of formation—ones as yet unossified and hence not visible in radiograms. (Bisgard, 1932, also described neurologic symptoms common in cervical arthritis.—Ed.)

Pathology. Hypertrophic spondylitis increases with advancing age.[382] Certain vertebrae are affected much more frequently than others. In his study of 126 vertebral columns with osteo-arthritis Shore [429] noted no involvement between the first and second cervical vertebral bodies, and very infrequent involvement between the eighth cervical and fourth thoracic levels. There were three marked " outcrops "—regions of most frequent osteophyte production: (1) the cervical outcrop, between the third and sixth (with peak between the fourth and fifth) cervical vertebrae, (2) the thoracic outcrop, increasing in frequency from the fourth to the ninth and tenth thoracic vertebrae, osteophytes then receding in frequency between the tenth thoracic and first lumbar vertebrae, and finally (3) the lumbar outcrop, most notable of all, with osteophytes most frequently between the third to fourth and fourth to fifth lumbar vertebrae. The three " minimum-points " were at the " anticlinal " vertebrae, which are supposedly balanced with a minimal tendency to slide or rotate and through which a plumbline would fall in the erect attitude of the body.

These curves of distribution of osteophytes from vertebral bodies were not quite the same as those found for osteo-arthritis of the small thoracic intervertebral joints.[408] In the latter, the four main outcrops were the cervical (whose peak was between the third and fourth cervical vertebrae, the cervico-thoracic peak at the cervico-thoracic joint), the thoracic (peak between the fourth and fifth thoracic vertebrae) and the lumbar (peak between the second and third lumbar vertebrae). Zones of minimal incidence were between the seventh, eighth and ninth thoracic and between the sixth and seventh cervical vertebrae.

Roentgenograms. According to Scott [428] sacro-iliac joints in " spondylitis osteo-arthritica " exhibit no pathologic changes roentgenographically, a sharp contrast to the constant changes in " spondylitis adolescens."

(This observation is at variance with general experience. Others, Zöllner, 1930; Smith-Petersen, 1932—cited by Keefer,[382] noted anatomic changes in sacro-iliac joints increasing with age.—Ed.) Several papers reproduced roentgenograms

of the pathologic changes in intervertebral disks which may lead to hypertrophic spondylitis.[400, 401, 402, 410]

Etiology and Pathogenesis. Varieties of trauma are considered the chief cause—occasionally acute trauma, more often chronic trauma of certain occupations, or of long-continued weight bearing resulting from man's erect posture.[382] The distribution of osteophytes of the thoracic intervertebral joints was interpreted by Shore [408, 429] as follows: the cervical outcrop is probably due to weight bearing in the joints of the already dorsiflexed cervical vertebrae; the cervicothoracic outcrop results from the use of the upper limbs, by movements of dorsiflexion transferred from the limbs to the thoracic skeleton and by associated action of the erector spinae muscles; the thoracolumbar outcrop is the result of weight-bearing in the joints of the dorsiflexed lumbar column and absorption of the lower thoracic vertebrae into the lumbar curve as lordosis is established.

Trauma alone, however, does not explain these changes satisfactorily, and trauma is but the last in a chain of circumstances which cause hypertrophic spondylitis. The series of events culminating in the excess trauma that stimulates osteophyte production is, as we have noted, now thought to include degeneration of intervertebral disks as the feature of primary pathologic importance.

Treatment. Accepting current ideas on pathogenesis it is difficult to see how removal of infected foci could help much, as it could not lessen trauma or restore the integrity of damaged tissue.[403] However, in spite of his conclusions on the general production of osteophytes by trauma, Shore believed some cases might be due to toxic or bacterial infection. In a case of severe "lumbago" with narrowed intervertebral disks and marginal osteophytes Shore isolated hemolytic colon bacilli (it is not stated from whence). Vaccine was prepared and given with "striking results." The patient was "cured" and subsequent roentgenograms showed that the intervertebral disks had recovered their proportions and osteophytes had "become static." (The case is mentioned without details.—Ed.) Good posture must be adopted so that facets won't have to carry weight.[407] Heat, rest, massage, and supports were approved. When conservative therapy was inadequate, more radical therapy was advised: traction, casts, spine fusion or facetectomy. Operative and non-operative indications and methods were reviewed by Kreuscher.[392]

Gout and Gouty Arthritis

A reawakened interest in gout is apparent. For 15 years only about three articles on gout have appeared annually in medical literature written in English. Last year, however, there were eight or more. The writers insisted that gout is not uncommon. The experience of their patients indicated that nowadays a case of gouty arthritis is much more likely to be called "rheumatic fever," "infectious arthritis" or "acute arthritis" than to be diagnosed correctly. Gout is seen with increasing frequency by those

on the alert for it. In England, three of every 1,000 insured workers become disabled thereby (Glover, 1924). Of workers at "hot occupations," (e.g. stokers) admitted to Buckley's [4] clinic for rheumatism, 8 per cent had gout. He suggested that excess loss of perspiration altered the saline content of tissues and the solubility of sodium bi-urate.

Clinical features of classic gouty arthritis were reviewed by Gupta,[432] Cohen,[433] Fitz,[265] Hench,[49, 106] Lockie and Hubbard,[434] Monroe,[435] Talbott, Jacobson and Oberg,[436] Volini and O'Brien.[437] Among features stressed were these: Gout may affect the poor, the vegetarians and teetotalers as well as the rich, the meat eaters and the alcoholics.[432, 433] Gout rarely affects females: 98 per cent of patients are males.[49, 106] However, four women with gout were noted by Monroe and by Talbott et al. The age at onset of gouty arthritis is generally after 40 years; however, in 28 per cent of Monroe's cases it was under 30 years. The onset was at the age of 10 years in one of his cases and at 12 or earlier in the case of another.[436] The first attack is likely to be in a large toe (in 74 per cent of one group [435]) but often a knee, ankle or other joint is affected and the great toe may long be spared. When the great toe is affected maximal tenderness is generally at its mesial surface.[106] A later, or even the first, attack may be polyarticular, with some tendency to migration. In spite of much pain and localized redness, attacks are often without fever or leukocytosis. Spine, hips and jaws which are rarely affected, were involved in some cases.[435, 486] Since olecranon bursitis occurs at least five times oftener in gout than in atrophic arthritis, its presence should suggest gout.[106, 437] The blood uric acid almost always becomes elevated, although not in some cases until late in the disease. It is occasionally normal even in a patient with tophi (Monroe [435]). It often returns to normal under adequate treatment but may remain elevated even though gouty arthritis is controlled (Cohen [433]). At a given time tophi are found in only 50 to 69 per cent of cases.[106, 435] They are easily and repeatedly overlooked until sought by one suspecting gout. A "tophus" is not a tophus no matter where it is located until it is opened and found to contain urates. Roentgenograms are generally of little value in early diagnosis, generally become "characteristic" only late in the disease. Attacks of acute gouty arthritis subside "rapidly or grudgingly." [435] Between early attacks complete functional restitution of joints practically always occurs. However, a few (12 per cent) of Monroe's patients were not entirely free of pain between acute exacerbations. When the acute attack is over, chronic symptomless gout still persists and must be treated.[49, 106, 437] "Proven gout" from the pathologic standpoint means tophaceous gout, but a diagnosis of "presumptive gout" (provable from the clinical standpoint) must be entertained in all patients without tophi who exhibit the characteristic pattern of gouty arthritis: early acute attacks (in one or more joints, with or without hyperuricemia) with complete remissions; later, of chronic gouty arthritis.[49, 106]

(Monroe's case 4, that of a male, is of special interest. The first attack at the age of 32 years involved hips and then knees, feet and many other joints including the jaws. After four months, recovery was "fairly complete." The diagnosis was rheumatic fever. Subsequently less severe attacks repeatedly involved practically all joints including the spine. Physical examination, at the age of 57, revealed tophi, hyperuricemia, swollen temporomandibular joints, fingers and ankles, and stiffened wrists, elbows, hips and knees. Roentgenograms of hands and feet showed "marked hypertrophic changes." In the absence of rheumatic carditis and with tophi ultimately present, Monroe concluded the first attack was also probably gout. Four months is very long for an initial arthritis of gout or of rheumatic fever. If all of this patient's attacks were of gouty arthritis, the involvement of jaws, hips, and spine makes it worthy of special note as we are unaware of any proved cases of gout in these joints in the literature of the past many years.—Ed.)

The report of Gupta is also of special interest. He had records of 250 cases of gout and noted "the existence of 700 to 800 untreated cases of gout" in Nepal, India, which has a population of 40,000 to 50,000—an admittedly astonishing incidence of 60 to 70 cases of gout per 1,000 population. This was all the more unusual since great numbers of the natives, including many with gout, were absolute vegetarians and teetotalers because of great poverty or their religion. Six cases were detailed.

(Comment thereon is in order: four of the six patients reputedly had "tophi," the authenticity of which would have been unquestioned had photographs of them or their contents been shown. It was not specifically stated that they were opened and examined. However, we are inclined to accept them as tophi since a characteristic history of gout was present in three of the four cases. One patient had "chalky concretions on ears and eyelids," and an eight-year-old boy who had had repeated acute podagra and "whose family had gout" presented tophi on ears and in nasal cartilages. Tophi on eyelids and in the nose have been reported, but they are most uncommon even in severe, chronic gout. Therefore, without more data one is skeptical. Patient 2 had acute attacks in great toes and knees with sciatica; his "mother, two brothers and a sister were gouty." Case 3 was that of a man without arthritis, whose radial neuralgia was considered gouty because of hyperuricemia and because atophan gave prompt relief after morphine and other drugs failed. Case 4 concerned a woman with a blood uric acid of 4.5 mg. per 100 c.c., "tophi," and a history of pain in her great toes. She had hypertension, interstitial nephritis and a recurrent bleeding tonsillar abrasion. A diagnosis of retrocedent gout was made since the "usual measures for gout" reduced blood pressure and stopped hemorrhages. The patient may have had gouty arthritis, but the diagnosis of retrocedent gout is debatable.—Ed.)

Bassler [488] reported gastrointestinal symptoms in 23 cases with "chronic and irregular forms" of gout. The symptoms were believed due to or associated with gout and included pyrosis, eructations, flatulence, constipation, heaviness and drowsiness after meals, abdominal and pelvic pain, colonic distress, colics and cramps, excess mucus in stools, nausea and anorexia. From these alone the diagnosis of gout cannot be made; it must be made on the condition of joints and the blood uric acid. "In gout the total uric acid per 100 c.c. of blood and urine combined is always above high normal. . . . Studies were made on 10 patients as to the uric acid and urea ratio using

1 to 55 as the standard and also on the alkalinity of the blood. . . ." (No figures or results are given to explain these statements.—Ed.) "The suggestion of the disorder comes from deposits of urates causing stiffness in the ligaments and are noticed (sic) in the feet and slightly less so in the hands." Bassler gave colonic instillations of oxygen for the intestinal toxemia of a "distinctly gouty woman." Within two weeks she was relieved of "night leg cramps; stiffness of knees and fingers improved markedly and she could flex the tips of her fingers to the palms for the first time in four years." Thereafter he treated with oxygen 22 cases of what he considered digestive manifestations of gout. "In all but five cases a strikingly quick result on the symptoms took place."

(No data of any sort are given concerning the history, sex, physical examinations, blood uric acid concentrations, presence of tophi, roentgenograms of joints or laboratory tests on intestines. It is impossible for us to conclude from the data given how many, if any, of the cases were of gout, and that the intestinal symptoms were relative thereto. In the case of the woman just mentioned, no proof is given that she had gouty arthritis and not chronic non-gouty arthritis. No figures are given to support the statement that oxygen instillations reduced the uric acid content of blood and urine.—Ed.)

One of Monroe's [435] patients regarded an attack of diarrhea and malaise as a regular warning that gouty arthralgia was soon to follow. Another of his patients on a regimen for gout got relief from gouty arthritis but not from persistent salivation and hawking, for which a diagnosis of 'gouty bronchitis' had been suggested. The incidence of vascular disease was definitely higher in his gouty than in his other patients with atrophic or hypertrophic arthritis. Although there was a basis for argument, Monroe concluded that "irregular gout" was a highly speculative affair, evidence for which was usually most inadequate. Volini and O'Brien [437] also concluded that the dyspeptic symptoms which Lichtwitz (1934) and others regarded as precursors of acute gout "are so much more frequently associated with gastrointestinal and gall-bladder disorders that they seem of little value as a warning sign."

(As one writer said, only one in four patients with gout receives a correct diagnosis; but it is also true that in some quarters only about one in four patients who receive a diagnosis of gout actually has the disease. Slocumb,[99] for example, found several European physicians making a diagnosis of gout in cases of Heberden's nodes, or of transitory, mild subdeltoid bursitis, or in certain cases of chronic arthritis with "gouty dyspepsia" without tophi, hyperuricemia, or history of recurrent acute attacks and remissions. One distinguished physician with a wide knowledge of classical gout expressed his feeling that solitary chronic arthritis of the second or third metacarpophalangeal joints of women or men was practically always gout even without hyperuricemia, tophi, or recurrent acute attacks: the only basis for the idea was admittedly his "clinical experience." It has been said that the accuracy of a physician's criteria for gout can be judged on the number of his patients who have tophi or are females. If more than 50 to 70 per cent of his patients have tophi he is too exclusive and is probably omitting cases of bona fide (even if pretophaceous) gout.

If less than 35 to 40 per cent have tophi or if more than 2 to 5 per cent are females he is too inclusive, diagnosing gout where it does not exist. Because tophaceous or even pretophaceous gout in females is very rare, it should be noted that the father of Fitz' [265] patient, also two brothers and a sister, had gout and "one of his daughters has a persistently elevated blood uric acid though she has never had true podagra." One of Gupta's six patients was a woman, and the mother, two brothers and sister of another patient were also "gouty." One of Bassler's patients was a "distinctly gouty woman." Only four of Monroe's 59 patients were females. One was reported as having a "degenerating tophus." Further investigation [212] led Monroe to conclude that the nodule was not a probable tophus, and that although the history was very suggestive of gout, the very low level of blood uric acid and the unsettled matter of the "tophus" made the diagnosis uncertain. All of which leads us to conclude that it is not always easy to decide when "gout" is truly gout, that the diagnosis of gout in females must be made with extra caution, and that, when it is made, full details in support thereof should be given.—Ed.)

Agents Which Provoke Gouty Arthritis. It is of diagnostic importance to remember that acute gouty arthritis frequently appears with changes of seasons (spring and fall); after gastronomic or alcoholic celebrations; after fixed festivals such as birthdays, Thanksgiving, Christmas or the Passover; after acute or even trivial trauma such as a day's automobile driving, and while patients are receiving certain types of treatment such as salyrgan or other strong diuretics for cardiac decompensation, liver extract for pernicious anemia, ergotamine tartrate (gynergen) for migraine or for the pruritus of icterus, and, very rarely, after insulin (Hench [49, 106]). Hench noted that gouty arthritis was frequently provoked by activities incident to a hunting or fishing trip (tight boots, rough walking, damp, and excesses in meat and alcohol). As a result some of his patients "had to be carried home—game, gun and gout."

Leukemia and polycythemia are not infrequently complicated by acute gout, as was lead poisoning formerly. Krafka [439] noted that any (hemolytic or hematonic) condition which tends to stimulate the erythropoietic system may provoke acute gout. Lead is an active hemolytic agent and every low blood count is compensated for by an increased marrow activity. Hemorrhages, "bleeding," and liver extract are marked hematopoietic stimulants. Bone marrow is stimulated, and an increase in erythrocytes results. Endogenous uric acid rises from the destruction of the extruded nuclei of the normoblasts in the maturation of erythrocytes. Acute gout ensues.

In line with the observation of others that starvation or high fat diets induce marked increases in blood uric acid concentration, Lockie and Hubbard [484] found that the administration of a high-fat, low-carbohydrate diet (fat 250 to 350, carbohydrates 30 to 50, protein 50 gm.) for five to seven days promptly provoked acute gouty arthritis in four cases but did not affect patients with non-gouty arthritis. In some cases blood uric acid rose markedly and the urinary uric acid content fell, but the symptoms provoked were not directly dependent on the altered blood uric acid. The induced attacks were promptly relieved by diets high in carbohydrates, low

in fat. The provocative diet was therefore proposed as a diagnostic test and it was concluded that diets high in fat and low in carbohydrates should be avoided for patients with gout. The wisdom of this advice was confirmed by Hench [106] who noted the development of acute gout in several patients whose bacilluria was being treated by the ketogenic diet.

(The diets of Lockie and Hubbard were not ketogenic as it is almost impossible to produce ketosis with a carbohydrate intake of more than 15 to 20 gm. It should be determined to what extent ketosis must be approached to provoke gout.—Ed.)

Within 12 to 120 hours after almost any surgical operation patients with quiescent (unsuspected) or active gout are prone to develop acute gouty arthritis. Coburn and Pauli [178] noted that surgical operations occasionally provoked a recurrence of rheumatic fever. Hench [49, 106] found, however, that the great majority of about 50 cases of acute postoperative arthritis were ones of acute gouty arthritis and approved the axiom: "In cases of acute postoperative arthritis (especially in males over 40 years of age) suspect gout." Clinical and chemical details of two such cases were given. (The provocative effect of surgical operations in gout is in striking contrast to the temporary benefit that almost any surgical operation may provide for patients with atrophic arthritis.—Ed.)

Laboratory Data. Two of Miller's[291] six patients had some degree of hepatic inefficiency as shown by levulose tolerance tests. Blood proteins in three cases of gout were as follows: albumin 4.0 to 4.4, average 4.2; globulin 2.2 to 3, average 2.5; total proteins 6.9 to 7.3, average 7.1 gm. per 100 c.c.[257] (In neither of these reports did it state whether tests were done during active gouty arthritis or quiescent gout.—Ed.) Roentgenograms in gout may not be characteristic and frequently simulate those in chronic non-gouty arthritis (Doub [11]).

Pathology. Galantha [440] described a new technic for the preservation and microscopic demonstration of urates in gouty tissues. The crystals therein were beautifully demonstrated. (Formalin dissolves urates promptly and gouty tissues fixed therewith will show no crystals, merely crystal clefts. Galantha's method uses absolute alcohol as a fixative.—Ed.)

Etiology and Pathogenesis. It is now commonly believed that an excess of urates alone is not the cause of gout but merely an index of the metabolic disturbance that causes it. As Ray [351] stated, the etiology of gout is very obscure and estimations of blood uric acid are of satisfaction only to those who still believe purine bodies are causes of gout. Observations supporting the idea that gout may be a more widespread disturbance of bodily equilibrium than a dysfunction of uric acid metabolism were made by Talbott, Jacobson and Oberg [436] who studied the electrolyte balance of two gouty patients: In one case 50 attacks were studied in 22 months, in another seven attacks in nine weeks. Changes in water and salt metabolism were as follows: diuresis began before any clinical or subjective evidence of gout was manifest. A negative sodium and chloride balance accompanied this diuresis and there was also an increased excretion of potassium, calcium, am-

monium, titratable acid, phosphate and urate. The previous observation of others that prior to an attack there is a decrease in urinary uric acid, was not confirmed.

(Statistical data presented deserve full consideration and may suggest new treatments. Those who have made metabolic studies, particularly on patients with gout who consider themselves "well" when the acute arthritis is over, will agree that the authors need make no apologies for having presented studies on only two cases, for the studies were very carefully made over long periods. Because of the continual shifts in electrolytes, the authors considered it doubtful whether a period of normal fluid and electrolyte balance of significant duration is ever observed in patients with gout. However in these two cases the frequency of attacks was so great [averaging an attack in one case every 13 days, in the other every nine days] that one might regard these patients as having, not acute recurrent gouty arthritis but chronic gouty arthritis with acute exacerbations. Studies should be made on patients with earlier, less active gout to see whether they demonstrate long periods with a normal equilibrium. The second patient was a woman. While the published report does not state that she had tophi, we are informed that she had numerous tophi and, a few days after thyroidectomy, severe, postoperative, acute gouty arthritis.[212]—Ed.)

Habitual use of alcohol was admitted by 62 per cent of Monroe's patients. That gout may affect vegetarians and abstainers from alcohol indicates that excesses of food and drink are probably only precipitating factors, not the cause of gout. The majority discount the factor of infection except as a provocative, but some (Gupta,[432] Willcox [441]) favor the infectious theory. Llewellyn's theory that gout is an allergic manifestation to specific proteins was attractive to Nisse [442]: "a focus of infection is likely to produce repeated attacks of gout by sensitizing a joint, already handicapped by a defective purin metabolism, to the effects of the bacterial antigen produced by the focus." A reverse sequence was suggested by Willcox [441]: "in gout there is often some chronic infection which has sensitized the body and which has caused the uric acid metabolism to be disturbed."

Treatment. The diet proposed for treatment by Lockie and Hubbard [434] contained 350 to 400 gm. of carbohydrate, 50 gm. of protein, and no more than 50 gm. of fat. Attacks of acute gout were relieved thereby. Pisani [443] independently noted the benefits of a high-carbohydrate intake in gout and administered glucose orally, rectally, or intravenously, depending on whether gout was active or quiescent. Joltrain [444] gave his patients skin tests with purine and non-purine containing foods and interdicted all foods to which the patient's skin reacted, as well as many purine-containing foods. Diet in gout is a matter of quantity rather than quality, according to Watson [445] who regarded the use of small amounts of presumably dangerous foods as harmless. The diet should be purine-free for three to four weeks after an attack; then it should be low in purine but high in non-purine containing proteins (milk, eggs, cheese).[49, 106, 433, 437] A common mistake is to stop treatment as unnecessary once the acute attack is over. Interval treatment is essential to prevent not only the otherwise almost inevitable return of

gouty arthritis, but to control the potentially fatal effects of gout on the cardiovascular and renal system. Therefore, such a diet should be continued indefinitely. For this reason also some advise the intermittent use of cinchophen (three consecutive days each week) long after the acute attack is over. Although the routine use of cinchophen provides some risk to the gouty patient, it is, according to Hench,[49, 106] a minor and justifiable risk which must be taken whenever gout cannot be controlled by diet alone (which is very often the case). The mathematical chances of gouty patients being seriously or even fatally affected with gouty nephritis, renal stones, apoplexy or coronary disease (the not uncommon complications of gout), although moderate, present a more real danger than the rather remote chance of a significant toxic effect from cinchophen. Cinchophen and neocinchophen were used by Volini and O'Brien but, when contraindicated, were avoided in favor of salicylates and glycine, the synergistic action of which reputedly increases urate excretion (Quick, 1933). Cinchophen was avoided by Cohen [433] in favor of colchicine given in small doses every fourth week between attacks.

Acute postoperative gout can generally be prevented, according to Hench [49] by the following regimen: for five to six days before and after operation the patient is given a purine-free, high carbohydrate diet, a generous intake of fluid, 7½ grains (0.48 gm.) of cinchophen, t.i.d., and enough sodium bicarbonate to alkalinize the urine constantly. If a patient with gout must have liver extract for an associated blood dyscrasia, the experience of Fitz' [265] patient should be recalled. He took orally four ampules of Lilly's liver extract No. 343 daily for three months without precipitating acute gout. Tired of eating liver, he was given one intramuscular injection, which was followed immediately by the worst attack of gout he ever had. Fitz quoted Minot to the effect that such provocation is rare. Another gouty patient with anemia had recently taken intramuscular injections of liver extract for several months without the development of acute gout or increased hyperuricemia.

A review [48] of results of fever therapy included the following: Berris' (1933) patient with chronic gout of three years' duration, who was unrelieved by various measures and was unable to walk for four months, obtained "complete relief" after six fever sessions, being able to walk without pain after the second session. Auclair was also credited with good results in the treatment of gout, but no details were given. Slot [42] found gold valueless in gout. A mixture of goose-grease, pig-fat, sheep-tallow and pitch "alleviates the gout in anyone. This goose-fat is worth more than any treasure," according to an amusing verse translated by Brooke [446] from a Seventeenth Century manuscript.

Cinchophen Poisoning. This was not reported in cases of gout last year. However, four patients with other diseases developed it. A woman with atrophic arthritis had "subacute yellow atrophy" after taking 30 tablets of

oxyliodide in 25 days. A Talma-Morison operation was done, at which time the condition of the liver was apparent; the patient recovered (Clarke and Settle [447]). A young woman whose primary disease was unstated, died several weeks after developing jaundice, the result of taking 30 tablets of Cinsa-Vess (5 grains, 0.3 gm., cinchophen; 1/200 grain, 0.0003 gm., colchicine per tablet) (Peluse [448]). A young woman with rheumatic fever died with acute yellow atrophy after taking 37½ grains (2.48 gm.) of cinchophen in five days (Fraser [230]). A man, aged 52 years, became jaundiced and died after taking for three months "a patent medicine containing cinchophen"; at necropsy hepatic cirrhosis but no central necrosis was seen. Isolated from the patient's urine was normal coproporphyrin, increased in amount because of damaged excretory power of the liver. This is considered the first report of the isolation of a porphyrin from the urine of a patient suffering from jaundice or hepatic disease (Watson [449]). Cases of acute yellow atrophy, some fatal, due to the use of "M.S.T." (Martin's specialized treatment) began to accumulate; it and two other patent nostrums, Morton's No. 1 and No. 2 (containing cinchophen or neocinchophen) were barred from the U. S. mails.[450] Gastric and duodenal ulcers have previously been produced in dogs by administering cinchophen. Schwartz and Simonds [451] found cats very susceptible, guinea-pigs moderately resistant, and rabbits very resistant, to massive doses of cinchophen; four of six cats but none of the other animals developed gastric ulcers. The undoubted production in humans of gastric or duodenal ulcers by cinchophen has not been noted clinically or at necropsy.

The Uric-Acid Problem. According to Beer [452] many (non-gouty) patients with highly acid urine develop symptoms of renal or ureteral colic with microscopic or gross hematuria from showers of uric-acid crystals, gravel or stones. Uric-acid gravel is a conglomeration of uric-acid crystals; the "stones" are rarely larger than "half the size of a pin-head." Passage of gravel produces the same symptoms as those occurring with the passage of sizeable calculi. Urate stones and gravel are invisible in roentgenograms. The similarity to calculus disease in the presence of "negative roentgenograms" has caused confusion and wrong diagnoses of nephralgia, sympathetic nerve disturbances of kidney or ureter, and stricture or kinks of the ureter. In Beer's cases uric acid in the blood was not increased. After a shower of gravel, one may see with a cystoscope minute calculi on the vesical floor or protruding from swollen, traumatized ureteral meatuses. Uric acid crystals redissolve in the bladder, gravel does not; after a shower of crystals, they can be seen in the bladder only rarely, but if a fresh specimen of urine is preserved three to four days in a sterile test-tube, the crystals become apparent as typical "brick-dust." Generally the treatment in such cases is reduction of protein, increase of vegetables, fruits and water in diet, and the use of alkalis. In three of Beer's cases colic, ureteral obstruction, anuria and severe constitutional symptoms developed, and were relieved only by cysto-

scopy and ureteral catheterization. In one case showers of crystals were actually seen shooting from a ureter.

(These patients presumably had neither gout nor the "gouty diathesis," but apropos of the tendency of acute gout to develop within the first six postoperative days, it is interesting to note that in Beer's first case colic, hematuria and ureteral obstruction occurred "about the fifth operative day" after appendectomy. One of us (P. S. H.) has observed "ureteral flash-colics" without other urologic symptoms in a few cases of gout and has collected brick-red uric-acid gravel. This recalls the pamphlets of an earlier century "On the gravel and the gout."—Ed.)

Normal values for uric acid in the blood were redetermined with the revised micro-Folin method (1933) by Berglund and Frisk.[453] The mean uric acid value for unlaked blood was 2.7 ± 0.07 mg. per 100 c.c. for 89 normal women, 3.2 ± 0.08 mg. for 43 normal men. These workers noted the effects of salyrgan, novatophan, euphyllin, caffeine, pituitrin and lithium urate on uric acid elimination in man. With normal or damaged kidneys they found a linear relationship between uric acid in blood and urine: the elimination index. Salyrgan increased uric acid excretion, not by altering the mode of urate elimination, but possibly by altering the state in which uric acid exists in blood. (Salyrgan influences plasma colloids.—Ed.) The effect of novatophan was somewhat similar; there was no correlation between dosage and effect on uric acid elimination. Euphyllin also augmented uric acid excretion. Caffeine produced no significant changes in blood uric acid or glomerular filtration. The effect of pituitrin was difficult to interpret: there was halving of the elimination index but changes in blood uric acid and in the glomerular filtration rate seemed insignificant. In light of these experiments the authors discussed the rôle of glomeruli and tubules in the secretion of uric acid and presented data to show that the concentration of uric acid by the kidney can be greater than that of blood.

Quick [454] found that after strenuous, but not after mild, exercise the excretion of uric acid, but not of creatinine, was markedly diminished; uric acid and lactic acid in the blood rose slightly but definitely. He concluded that the diminution of uric acid excretion was due to excess production of lactic acid. Since neither lactic acid nor strenuous exercise apparently affect renal function, the uric acid retention is somehow linked with the metabolism of lactic acid, with which liver is concerned. Hyperuricemia in eclampsia, chloroform poisoning, cardiac failure and pneumonia result from the increased blood lactic acid that occurs in these diseases. (This report suggests that patients with quiescent gout might provoke an attack by strenuous exercise.—Ed.)

Cinchophen presumably mobilizes uric acid in human tissues and increases urinary uric acid 70 to 330 per cent. The administration of cinchophen generally causes (partial) evacuation of tissue-urates in about two to three days, after which additional doses do not augment uric acid excretion further. Fürth and Edel [455] attempted to discover whether the use of sufficient doses of phenyl cinchoninic drugs would completely evacuate rat's livers of their uric acid content. On the diet used the normal uric acid content of

rat's liver was rather constant, about 6.5 ± 1 mg. per cent. On administering cinchophen and tolysin there was an equal and marked reduction, not a complete evacuation, of hepatic uric acid to an irreducible minimum of about 1.5 mg. per cent. Although a maximal effect was obtained by about 0.01 gm. of the drugs daily per kg. of body weight, noticeable effects were obtained by 0.008 gm. per kg. daily (corresponding to a dose for man of only one-tenth of a single dose of 0.5 gm., 7½ grains).

Although the excretory effect of cinchophen and tolysin was the same, the former was much more toxic to rats, as determined by a much greater loss of body weight.

(These experiments suggest that cinchophen and tolysin may be clinically effective in much smaller doses than now used.—Ed.)

Of interest also are the studies of Matsuomoto [456] regarding the effect of mechanical and chemical damage to kidneys on the excretion of uric acid by the liver (into bile) of rabbits. In general, there was an augmented, possibly compensatory, excretion of uric acid in bile.

In rats, Borsook and Jeffreys [457] found that purines are converted into uric acid chiefly by liver and intestinal mucosa. Both these tissues actively convert guanine, xanthine and hypoxanthine. Mucosa alone converts adenine to any extent. Kidney and spleen have only a moderate, and striated muscle very little, effect on these purines.

Psoriatic Arthritis: Arthropathia Psoriatica

Two views exist regarding psoriatic arthritis: that it is a special entity, or that it is ordinary atrophic arthritis in a person who also happens to have psoriasis. Psoriasis may of course occur quite independently of a coexisting affection of joints and be only casually associated with any kind of arthritis. Thus it is not uncommon to see patients with atrophic or hypertrophic arthritis, or even rheumatic fever, with an entirely unrelated psoriasis. Because these incidental associations have erroneously been described by some as psoriatic arthritis, the existence of a true syndrome of psoriatic arthritis has been vigorously denied by many and the issue clouded. Certain features of psoriatic arthritis are quite distinct; one feature is practically pathognomonic according to Hench.[106] Except in one anatomic situation, the appearance of psoriatic arthritis is quite like that of mild or moderately-advanced, only occasionally severe, atrophic arthritis, and is indistinguishable from it objectively or roentgenographically. In one regard, at least, psoriatic arthritis is rather unique. It may involve knees, ankles, feet, elbows, wrists and hands, but it has a special tendency to involve the terminal joints of fingers and toes, with or without involvement of other joints of fingers and toes. Furthermore, the nails adjacent to affected, terminal phalangeal joints of fingers and toes practically always exhibit definite psoriatic changes. These differentiating points are illustrated in photographs (Hench [106]). Terminal joints of fingers and toes are

rarely involved in atrophic arthritis, as a rule only in the most severe cases and then only late. Terminal joints of fingers in hypertrophic arthritis are of course commonly affected with Heberden's nodes, but the terminal joints of toes are strangely exempt. Of diagnostic value, then, is the distinction that, in psoriatic arthritis, terminal joints of fingers and toes are commonly involved early in the disease, with psoriasis of adjacent nails. When these joints are not (yet) involved, psoriatic arthritis in other joints must be diagnosed by other features.

Psoriatic arthritis rarely comes with the first or with a mild bout of psoriasis. It usually attends a later or severe bout, when the patient has become careless in treating the skin lesion. In early phases of mild psoriatic arthritis a parallelism exists to some extent between the lesions of skin and those of the joints—when the skin is worse, arthritis appears; when the skin clears up spontaneously or under treatment, arthritis may diminish or disappear, even when the skin alone is treated. In severe or recurrent psoriatic arthritis articular symptoms may persist; the arthritis adopts its own rhythm and may be only partly relieved by measures for the skin.

Boots [84] did not recognize psoriatic arthritis as an entity; it is not included in his classification and he stated: "(in rheumatoid arthritis) psoriasis is not uncommon and has been referred to as psoriasis arthropathica." His colleague, Dawson,[103] took a more equivocal stand. Although he did not classify it or separate it definitely he stated, " the association of psoriasis in rheumatoid arthritis cannot be regarded as a mere coincidence."

(In the early stages of psoriatic arthritis, joints may sometimes recover function and the articular disease become inactive to a degree and with a speed not expected in atrophic arthritis. Boots and Dawson both showed photographs of the same young girl. Boots labelled it " Rheumatoid arthritis in a child [Still's disease]. Note fusiform fingers and psoriasis." Dawson labelled it " Psoriasis arthropathica." The condition of the terminal joints is not well seen in the photographs, so that the reader cannot venture an opinion on which form she may have had, but it may have been psoriatic arthritis as it is noted that she recovered to an unusual extent.—Ed.)

The main treatment for psoriatic arthritis is control of the psoriasis, with such additional routine measures for joints as are necessary. Hench favored Goeckerman's (1925, 1931) treatment of the skin: applications of White's crude coal-tar ointment and ultraviolet (quartz) irradiation.

Several general articles are noted, though they did not mention psoriatic arthritis: one on psoriasis as a possible allergic manifestation,[458] and a review of the modern treatment of psoriasis.[459] Sperry [460] used large doses of theelin intramuscularly in repeated courses to control but not cure severe psoriasis. Elson [461] considered psoriasis an enzyme deficiency disease: " Massive doses of pancreas extract will cure psoriasis." Two of Schwartz' patients [462] were benefited by the intramuscular use of colloidal manganese. According to Thurmon [463] " the more severe or extensive the psoriasis the more gratifying is the result obtained with intravenous organic sulphur."

Hemophilic Arthritis

Hemophilic arthritis may occur with each of three types of hemophilia: (1) true hereditary hemophilia, in which the bleeding tendency is a recessive sex-linked characteristic appearing only in males and transmitted only by females; (2) hereditary pseudohemophilia, in which the bleeding tendency is a dominant sex-linked characteristic and an affected mother or father may beget affected children of either sex; and (3) sporadic or spontaneous hemophilia, cases of apparently true hemophilia in which no hereditary bleeding tendency can be proved. Three patients with hereditary pseudohemophilia, two sisters and the son of one, all with recurrent hemarthrosis, were seen by Handley and Nussbrecher.[464] Family records, clinical and laboratory data, and the genetic relationship of the disease to true hemophilia were discussed. With the knowledge that true hemophilia has never been proved to exist in females, diagnoses were made as given, but the possibility was considered that these sisters might have had true hemophilia, the first homozygous hemophilic females recorded.

Two cases of sporadic hemophilia with arthritis affecting boys were reported by Marr and Herrmann.[465] The brother of one had died of hemorrhage, but no other evidence of hemophilia was found in either family. Congenital syphilis has been considered the cause of sporadic hemophilia; one of these patients had it, the other did not. Theories on etiology were reviewed.

The roentgenographic characteristics of hemophilic arthritis were summarized by Buus [466] and were as reported in previous reviews.[1, 2] A feature "not described before" was "characteristic sharp angulations in the joint-surface, which later developed into an abrupt rectangular break in the surface, so that part of the latter sinks to a lower level."

The pathology of articular tissues was summarized by Buus, and that of hemopoietic (but not articular) tissues in three fatal cases was described by Custer and Krumbhaar.[467]

Treatment. Of supreme importance is the control of hemorrhage. Blood transfusions were considered by some the most effective treatment.[464] Vine's horse-serum treatment was helpful in one case,[464] produced a severe reaction in another.[465] Marr and Herrmann [465] used several agents in two cases of recurrent hemorrhages. Best results were obtained by intramuscular injections of the patient's own blood. Blood transfusions were helpful, but intramuscular injections of the patient's or another's blood avoided the necessity of blood-typing. Good results were noted with protein sensitization by subcutaneous injections of sheep serum, by intramuscular injections of whole ovarian extract, or of blood from women at the beginning of menses or when pregnant. However, intramuscular injections of normal male blood were equally helpful: therefore, results did not depend on a high theelin content of blood. Thus Birch's theory that hemophilia results from inadequate female sex hormones was considered unproved by these workers

and others.[468, 469] Chew and his associates [470] studied for about a year two hemophilic patients, first untreated, then treated with estrogenic substances by mouth and subcutaneously, corpus luteum hormone intramuscularly, and the gonad-stimulating hormone from urine of pregnant women subcutaneously. The use of these hormones did not alter the coagulation time or benefit the clinical condition. No relationship existed between blood coagulation and the amounts of urinary estrogenic substances recovered. There was more of the latter in urine from untreated hemophilics than from normal males. At times, the coagulation time of patients was greater with treatment than otherwise.

McFarlane [471] and Barnett [472] reported further experience with Russel's viper venom which they considered (1934) the most effective local hemostatic available. The venom possesses remarkable potency as a coagulant in "almost fantastic dilutions." In a dilution of 1:1,000,000,000 it will coagulate hemophilic blood in six minutes. The venom is used in a dilution of 1:10,000 in physiologic saline solution and is non-toxic and non-irritating. Wounds should be carefully cleaned and dressings soaked with venom solution applied; these should be kept in place and then left alone as much as possible. Alveolectomy, tonsillectomy, prostatectomy were done safely by this means. Peck, Crimmins and Erf [473] regarded the venom of Bothrops atrox (Fer-de-lance) cheaper, more available and more effective than Russel's viper venom. Optimal dilution of the former was 1:10,000. Moccasin venom and a tissue extract (rabbit's lung) were ineffective.

In prophylaxis, a high-protein diet, much gelatin, and raw liver, and a diet high in vitamin B, were used by Marr and Herrmann.[465]

Allergic, Metabolic and Endocrine Arthritis

These three "diseases" are the current ghosts of rheumatology. Their names continue to be mentioned here and there in the literature, but their form and substance are most changeable and wraith-like. One writer materializes them in the form of atrophic arthritis; in another reincarnation they may resemble hypertrophic arthritis or some other articular disease. Although heavily cloaked in conjecture and shrouded in uncertainty, they are quite respectable ghosts and sometimes appear in the best company, being approved of by scientists of standing. And it is quite possible that, in time, any one or all of them may be born with a registered name and material body, definite in their clinical picture, etiology and pathology. All the recognized arthritides have had to struggle through years of embryonic life before they were born and finally accepted.

"Allergic Arthritis." Almost every type of joint disease has been considered an allergic reaction. Some regard food, others bacteria as offending antigens. Some believe the arthritis is actually caused by allergic reactions. Others admit allergic manifestations are present but regard them as of secondary significance, symptoms and not the cause of the disease. Many

writers do not make the distinction clear but just discuss this or that type of arthritis as "allergic." The "allergic phases" of various arthritides were briefly noted by Brown [214] who reminded us of Turnbull's (1924) views on chronic arthritis from food allergy. We have noted arguments for and against the (bacterial) allergic nature of rheumatic fever and atrophic arthritis. Intermittent hydrops is regarded by many as an allergic arthritis from unknown (food or bacterial) antigens. Serum sickness was again mentioned as the prime example of allergic arthritis. (As a matter of fact most allergists do not consider it an "allergic" but an "anaphylactic" arthritis, an antigen-antibody reaction and not true allergy.—Ed.) Contributing no new data Brown argued that "in every case of arthritis" the likelihood of food or bacterial allergy should be considered and skin tests should be made with food and bacterial antigens. Offending foods should be avoided and patients should be vaccinated against offending bacteria.

(Most physicians do not accept suggestions such as these because of the notorious unreliability and difficulty of evaluating skin tests to food and bacteria, and because of the rarity of undoubted clinical examples of allergic arthritis in which the food or bacterial antigen was definitely identified by provocative and therapeutic tests. —Ed.)

Myers [39] suggested the following as a case of "allergic arthritis":

A 34 year old man had had attacks of pain, redness and swelling in one or both feet each fall for three years. The first metatarsophalangeal joints and dorsum of the feet were chiefly involved. Attacks came suddenly, lasted 5 to 10 days, and then subsided. The present attack affected the right foot and great toe first, 6 days later the left foot and great toe. Erythematous tender areas were noted particularly over the medial aspect of the left metatarsophalangeal joint and dorsum of the foot. After two days on rest and salicylates the pain disappeared; swelling left three days later. Because the patient had had recurrent asthma each winter for four years, hay fever each fall ("late August until late October") for two years and chronic sinusitis for several years, and was "skin-sensitive" to pollens of ragweed and goldenrod, Myers suggested that "the arthritic symptoms were a response to an allergin" (inferring a pollen?—Ed.).

(Data are incomplete but suggest acute recurrent gouty, not "allergic," arthritis. The seasonal incidence (each fall), rapid onset, involvement of great toes, erythematous tenderness at the mesial aspect of great-toe joints, the rapid full joint recovery, —all are compatible with gout. Blood uric acid was not mentioned. The right foot was attacked October 7, the left October 13. Had the patient's arthritis been related to pollen one might expect it to appear in August or September, not at the end of the hay-fever season. Furthermore, arthritis antedated the asthma by three years and the hay fever by five. Skin tests were done with pollens, not with bacteria from sinuses. No provocative tests with presumably related allergens were done. Had allergic arthritis been suspected, response to epinephrine might have been more immediate and instructive than to salicylates. The problem of "allergic arthritis" would seem to be confused rather than clarified by such incomplete studies.—Ed.)

The question of "articular or periarticular hives" is raised by the case report of Dubbs.[474] An elderly woman with "mild recurring attacks of atrophic arthritis" and spindle deformity of finger joints developed "cold

allergy " in exposed skin, the short (5 to 10 minutes) attacks of which added other symptoms unrelated to her arthritis, such as wheals, tingling, itching, and redness, and swelling of the fingers, back and neck. These symptoms were abolished by administration of epinephrine. Dubbs considered the reaction essentially cutaneous and subcutaneous, not articular or just periarticular.

" Metabolic Arthritis." This term has never been satisfactorily defined. By it one writer means " atrophic," another " hypertrophic " arthritis. Still others mean " gout " or " articular pains with hypo- or hyperthyroidism." Under the broad definition of " metabolism " many if not every arthritis is a " metabolic " arthritis, but by a narrower definition it would be an arthritis due to some recognized abnormal metabolism of food. No definite consistent metabolic error has ever been identified with any of the arthritides except gout and alkaptonuria and, even here, the nature of the fault is very obscure. The year's literature added nothing to justify the term.

" Endocrine Arthritis." This term has been variously used also as a synonym for almost every type of arthritis. Particularly confusing is the term " menopause arthritis " which is applied by one writer to cases of atrophic, and in other instances to hypertrophic, arthritis appearing near the menopause. Others give it a special meaning: a villous synovitis of knees in women about the menopause, but definitive clinical and pathologic data are not at hand. Since most of the arthritides are general diseases, sometimes with extensive secondary physiologic disturbances, it is not surprising that disturbances in endocrine function are found, but no consistent etiologic relationship between any form of arthritis and any recognizable endocrine disturbance has been proved.

Robinson [349] accepted Llewellyn's conception of " menopause arthritis ": villous synovitis in traumatized joints, especially knees, with hypothyroidism prior to the menopause. " It may come on several years before or round about the time of the cessation or several years afterwards." (The vague time relationship alone would seem to refute the appropriateness of the term.—Ed.) Periarticular fat pads give an appearance of joint enlargement; the cavity is distended with synovial proliferations or fluid. The joints creak and reveal lipping of bone in roentgenograms. Robinson (1926) reported cases affecting young women with amenorrhea which were relieved when menstruation was restored by intrapelvic diathermy, of which he again approves. To many the syndrome is identical with hypertrophic arthritis, but Gray [251] accepted it as a separate entity.

The relationships between chronic arthritis, hyperthyroidism, and myxedema were discussed by Monroe.[296] According to another [295] atrophic and hypertrophic arthritis are badly mixed up with the endocrines.

Relation of Arthritis to Parathyroids; Parathyroidectomy for Arthritis. Because he found hypercalcemia and decreased electromuscular excitability in some cases of " ankylosing polyarthritis and spondylarthritis," Oppel (1926) suggested that these diseases were due to hyperparathyroidism and

proposed parathyroidectomy therefor. The idea was advanced by certain French and Russian workers and by Ballin and Morse (1931) in this country, but it has been sharply denounced by many. Schkurov [298] reported results of "parathyroidectomy" in 83 cases (or 86, both figures are given) of "chronic rheumatic polyarthritis and spondylarthritis." Values for blood calcium before operation ranged from 8 to 17 mg.; after operation 7 to 15 mg. per 100 c.c. Blood calcium before and after operation, respectively, was below 9 mg. in 6 and 16 per cent; between 9 and 10.9 mg. in 52 and 55 per cent and 11 mg. or above in 42 and 29 per cent. Thus there was a postoperative shift from high to normal and from normal to subnormal values for calcium. Immediate results from the operation were noted "in all cases": less muscle and joint stiffness and pain, and increases of 10 to 55° in joint motion. The results six months to four years later were noted in 40 cases. They were "good" (subjective and objective improvement) in 55 per cent, "satisfactory" (subjective relief only) in 35 per cent. Four patients were unrelieved or were worse. Schkurov concluded that parathyroidectomy cannot affect existing ankylosis but prevents ankylosis and will "do away with rigidity of joints."

(Containing conflicting statements, poor arithmetic, shifting premises and conclusions impossible of acceptance, this report is open to sharp criticism. It is our opinion that if any significant relief was obtained, it was not from parathyroidectomy or any associated alteration in calcium but was in all likelihood entirely non-specific—the temporary relief which may follow, sometimes dramatically, almost any surgical operation. Schkurov reported hypercalcemia in 42 per cent of his cases. The method is not stated and the figures seem questionable since many excellent investigators have failed to find hypercalcemia in arthritis, except in rare cases. No metabolic studies, data on blood phosphorus or phosphatase, or urinary calcium and phosphorus were reported. He says: "An important objective effect of parathyroidectomy is the decrease of blood calcium." But 52 per cent of his patients had a normal blood calcium before operation and only 3 per cent more [55 per cent] had normal values after operation. Parathyroidectomy was done in cases with and without hypercalcemia, yet admittedly results were the same in each group. But because some who had normal blood calcium were benefited, he then advocated surgery for patients with rigidity of joints or a "tendency to ankylosis" even if the calcium was normal.

He stated subjective improvement was obtained "in all cases," but this would then include one case in which "the patient did not feel any improvement for an entire year, but afterward pain subsided and mobility of joints was increased." Although "all" patients obtained immediate improvement, results six months to four years thereafter were only "good" in 55 per cent, and if the following is a representative case this figure is also open to question: A young woman had "contractions of the hip, both knees, elbows and wrist joints. Before operation she walked in a squatting position with the help of legs and hands—almost creeping. . . . After parathyroidectomy and subsequent treatment by extensions" there resulted "an almost complete correction of all deformities" and "full restoration of all movements of joints." It is difficult to believe this, or certainly to ascribe it to parathyroidectomy rather than to manipulations.

The statement most destructive to his proposition was that in 23 [or over a fourth] of the 83 cases "histologic examination [of tissue removed at operation] did not

show any evidence of parathyroid gland tissue," in spite of which several had subjective improvement and a lowered calcium. We cannot understand why he included them in a discussion on parathyroidectomy and statistical results therefrom. Obviously, results could not possibly be from parathyroidectomy [which wasn't even done in 28 per cent] or from the inconsistent shifts in blood calcium. In some cases edema of the feet completely disappeared after operation, but in at least one case it reappeared when the patient began to walk. This too suggests that results were nonspecific from an operation, from bed rest, relief of trauma and of static edema.—Ed.)

At first Schkurov suspected the results were due to suggestion, not to parathyroidectomy. He discarded this idea when autohemotherapy without parathyroidectomy gave no relief. Having also noted relief even when removed tissue contained no parathyroid tissue, Simon and Weil (1932) ascribed it to removal of thyroid tissue or of fat. This led them to make a simple skin incision without touching the parathyroids: results were also satisfactory. Bach [297] and Rankin [475] criticized Oppel's work, stating that no metabolic studies were done, that the diagnosis was made on single determinations of serum calcium, that at operation parathyroid tissue was not always removed or even identified, and that symptoms often recurred rapidly. The fact his results were as good whether parathyroid tissue was removed or not, Oppel considered was because operation produced parathyroid ischemia by interfering with the nerve and blood supply. According to Bach equally good results were obtained by Weill who merely exposed the glands, and by Simon who applied chemical irritants to the thyroid gland. Those who have performed parathyroidectomy have claimed that if the operation is successful, on the same evening or on the day after, pain and periarticular swelling are markedly diminished and movements which were formerly painful become painless.

(These same dramatic, but generally temporary, results have been reported after removal of teeth, tonsils, appendix, gall-bladder, spleen, sympathetic ganglions, and other tissues. Bach [297] noted similar dramatic results after thyroidectomy.—Ed.)

Authors with a large experience with undoubted hyperparathyroidism in this country (Bauer,[476] Bauer and Camp,[477] Lahey and Haggart,[271] Mason and Gunther,[478] Rankin [475]) all agree that parathyroidectomy cannot be sanctioned for arthritis and that " ankylosing arthritis " is not from hyperparathyroidism. One cannot even justify exploring the parathyroid glands of patients with skeletal changes until one has obtained chemical or pathologic evidence that such changes are due to hyperactive parathyroid tissue. In a study of 200 patients with atrophic arthritis Lahey and Haggart found no evidence whatever of hyperparathyroidism. Serum calcium and phosphorus were consistently normal and roentgenograms never revealed features of hyperparathyroidism. In 100 cases of atrophic and hypertrophic arthritis Hartung and Greene [258] found no evidence of hyperparathyroidism: in 97 per cent the blood calcium was normal.

Although the two diseases are unrelated, the skeletal pains of hyperparathyroidism are sometimes diagnosed " rheumatism " or " arthritis." In

hyperparathyroidism the shafts of bones are involved in local and generalized softening, destruction and cyst formation. Current reports gave details of about 50 cases. In at least 14 symptoms included pains in legs, arms, thighs, and lower back, and sometimes in hands and feet. Some of these cases were frankly considered arthritic until the characteristic roentgenographic and chemical alterations of hyperparathyroidism were discovered. The latter are fully discussed in several good papers (Albright,[479] Bauer,[476] Bauer and Camp,[477] Borg,[480] Castleman and Mallory,[481] Cuthbertson and Mackey,[482] Lahey and Haggart,[271] Leff, Blanchard and Peabody,[483] Mason and Gunther,[478] Quick et al.,[484] Rankin,[475] Robbins,[485] Taylor [486]).

Miscellaneous Types of Joint Disease

Hemorrhagic Villous Synovitis due to Xanthoma. Kling and Sashin [487] reported one case. A knee was painful for two years. Hypercholesteremia (238 to 288 mg. per 100 c.c.) was repeatedly present. Presumably a disturbance of lipoid metabolism caused lipoid precipitation and xanthoma formation. Synovectomy gave relief. Twenty cases previously reported were reviewed: symptoms resemble those of inflammation or internal derangement. Preoperative diagnosis may be made by finding an increased bilirubin and cholesterol content in the effusion.

Synoviomas (Benign and Malignant). Tumors of articular structures other than bone are rare. Synoviomas apparently originate from capsule or synovial membrane of bursae or joints, usually a knee. Less than 100 synoviomas have been reported (Razemon and Bizard, 1931) of which 43 were benign, 29 malignant. They may grow slowly and be regarded as "synovitis" for years before being correctly diagnosed. Amputation is often necessary. Coley,[488] Wagner [489] and Adair [490] reported several cases, and discussed their pathology and treatment. A malignant synovioma may invade bone, but it does not produce osteoid tissue although it has the objective characteristics of a bone tumor. Hodgson and Bishop [491] saw one affecting a man aged 28 years: his left knee was affected by a rapidly-growing tumor which soon metastasized to adjacent skin and lymphatics. Roentgen therapy and Coley's toxin were useless; the patient died in seven months.

Anomalous Synovial Cysts. Black [492] found two such cysts during classroom dissection. One cyst, 18 by 15 by 10 mm., was on the dorsum of the hand of a young laborer, between the first and second left metacarpals, and was inconspicuous until superficial fascia was removed. It did not connect grossly with synovial membrane of joints or tendon sheaths. The other cyst (16 by 10 by 8 mm.) formed an obvious swelling on the medial side of the fourth left phalanx proximal to the first interphalangeal articulation. It originated probably from a knife-stab.

Tenosynovitis. This most often affects a wrist or the peroneal tendons in the leg. Splints on lower extremities are cumbersome. Fieldman [493]

recommended the use of Unna's Paste Boot such as is used for varicose veins. It produces the least limitation of motion.

Cysts of Fibrocartilages of Knee Joint. Fifty cases reported to 1930 were reviewed by Taylor [494] who reported four more. Cyst formation in menisci are commoner (72 per cent) in men than in women (28 per cent), in external more often (82 per cent) than in internal cartilages (18 per cent). Trauma is the usual cause. Menisci become contused. A degenerative process in fibrocartilages results in multilocular cysts. Symptoms are localized pain, swelling and sometimes stiffness. Treatment is removal of the entire cartilage. Lesser procedures (removing or curetting cysts) are followed by recurrences.

Leukemia Resembling Rheumatic Fever. Some children with leukemia have fever and migratory joint pains without visible inflammation or roentgenographic changes. Others have acute arthritis with inflammation, roentgenograms showing focal areas of bone absorption, periosteal elevation and other changes. When cardiac murmurs from anemia are present and enlargement of lymph nodes and spleen is absent, the condition often resembles rheumatic fever before the blood picture becomes definite. Diagnosis may be suspected from the lack of effect of salicylates; it is eventually made on the appearance of abnormal leukocytes in blood. Three new cases of lymphatic leukemia resembling rheumatic fever affecting children were recorded by Smith.[197]

Keratodermia with Arthritis. Hyperkeratosis of skin and nails with arthritis may occur in gonorrhea—keratodermia blenorrhagica. Patel [495] saw an unusual case of keratodermia and arthritis affecting a Mohammedan boy without history, signs, or symptoms of gonorrhea: this boy, aged 9 years, noted painful swelling of several joints and painless nodules on his legs. Recurring fever, progressive cachexia and arthritis developed. Examination two years later revealed arthritic dislocation of the right knee and a wrist, flexion deformities of an elbow, both hips and left knee, huge rupia-like keratoid masses of growth on both legs—painless, hard to touch and brownish, and hypertrophy of nails. There was no evidence of syphilis. Interesting photographs were shown.

Mycotic Infections. Meyer and Gall [496] reviewed 60 reported cases of mycosis of the spine: 47 from actinomycosis, 12 from blastomycosis and one from sporotrichosis. Mycotic spondylitis is generally secondary to a primary respiratory or intestinal focus. Vertebrae are infected either by direct contact with a suppurating focus (in which case the external surfaces of vertebrae are eroded), or by vascular metastasis (in which case bone destruction is central and surrounded by a condensed ring of bone). Symptoms may be slight or marked. In these 60 cases a clinical diagnosis was made in only nine. Diagnosis is very difficult and not often made until late in the disease or until death. Mortality was 90 per cent.

In mycotic spondylitis involvement of intervertebral cartilages and the formation of osteophytes and periosteal inflammation are not generally seen.

The disease is generally mistaken for Pott's disease, from which it can be differentiated as follows: in mycosis the angular deformity typical of Pott's disease is most often absent because of the capsule of dense bone which surrounds the destroyed area and prevents flattening of vertebral bodies. Mycosis reveals multiple sinuses, more destructive invasion and a more rapid opening of abscesses than in Pott's disease. The skin lesions in mycosis are characteristic. Roentgenograms in mycosis show the following, none of which are often seen in Pott's disease: cortical erosion of vertebrae, also erosion of articular processes and pedicles, and cavity formation in the cancellous portion surrounded by a zone of increased density.

About 45 cases of Torula infection in man have been reported. Usually the nervous system, rarely the skeletal system, is involved. A young man seen by Kessel and Holtzwart [497] bruised a knee slightly. It became increasingly painful, swelling, effusion and flexion deformity ensuing. At arthrotomy Torula organisms were recovered, and animals inoculated therewith developed lesions. The patient developed Torula lesions of both breasts, but these responded to roentgen therapy. The granulomatous condition of the knee did not respond to treatment and amputation was necessary a year later.

Arthrokatadysis of Hip Joints. Levinthal and Wolin [498] reported five cases. This imposing name means "subsidence or sinking-in of a joint." It is not a specific disease but a feature which may occur "in osteo-arthritis, gout, gonorrhea, syphilis, tuberculosis, trauma or endocrine disturbances." It was previously called "osteo-arthritic protrusion or intrapelvic protrusion of the acetabulum (Otto pelvis)." The characteristic feature is protrusion of the acetabulum into the pelvis and a narrowed hip joint space. It results from weight bearing and muscle pressure at the diseased joint. The femoral head bores its way through a weakened acetabulum into the pelvis. Symptoms are those of progressive chronic arthritis. Roentgenograms are characteristic: deepened acetabulum, thinning of the medial and inferior wall, eburnation, and narrowed space. If conservative treatment (heat, massage, traction) fails, casts or braces, arthroplasty, or arthrodesis, are indicated.

"A Syndrome of Unknown Etiology." Christian [499] summarized reports of two patients who had long continued fever with inflammation of serous and synovial membranes (pleurisy, pericarditis, arthritis) and who eventually died of glomerulonephritis. Numerous laboratory tests failed to elicit the causal infection. The two cases were previously described by Tremaine (1934) as "Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis." (Christian noted that some patients have skin lesions suggestive of lupus erythematosus. To us the cases seem to be of acute, lupus erythematosus disseminatus, one with and one without skin lesions.—Ed.)

Acute Postoperative Arthritis. Some cases were identified by Coburn and Pauli [178] as recurrences of rheumatic fever provoked by surgical operations. Of cases of acute postoperative arthritis seen by Hench [49, 106] a few were of rheumatic fever but the great majority were gouty arthritis, clinically

proved by past histories, physical and laboratory signs of gout, and response to treatment.

Diseases of Muscles, Fibrous Tissue and Bursae

Introduction: Classification. A study of diseases of muscles is largely an excursion into the unknown.[500] Various classifications of such diseases are in vogue.

Shelden [500] classified them briefly into: (1) conditions in which disease of muscles is incident to a general infection (for example, rheumatic fever); with convalescence muscles recover rapidly and no special attention is paid them; fortunately, the muscular system generally has a high degree of immunity to infections which affect other organs, hence muscles are but infrequently and transiently involved; (2) diseases peculiar to muscles themselves, which are rare but important and include acute and chronic (true) myositis, dermatomyositis, myasthenia gravis and the neuromyopathies. Ornsteen [501] approved Batten's (1904) classification of inflammatory diseases of muscles: (1) primary infections, (*a*) acute polymyositis, dermatomyositis, hemorrhagic myositis, polymyositis with erythema multiforme and urticaria, and pseudotrichinosis, (*b*) neuromyositis, (*c*) tuberculous myositis, (*d*) syphilitic myositis, and (*e*) myositis with trichiniasis; (2) secondary infection in the course of acute or chronic disease, (*a*) myositis with specific fevers (typhus, typhoid, smallpox), (*b*) infective myositis with pyemia, infective endocarditis, glanders, gonorrhea, puerperal infection, infected wounds, actinomycosis, erysipelas, etc.; and (3) myositis with special terminal lesions, (*a*) myositis ossificans progressiva, (*b*) general or localized myositis fibrosa.

(The necessity of using a classification 32 years old is evidence of lack of progress in this field. This classification does not specifically mention the common form of "myositis," every-day muscular rheumatism (intramuscular fibrositis). In discussions of "Myositis" one must distinguish between (1) "true myositis," parenchymatous diseases of muscles where definite primary pathologic lesions of muscle cells are seen, and (2) interstitial muscle disease, in which primary lesions are almost if not entirely in supporting fibrous tissue and in which muscle cells are rarely ever involved in demonstrable disease except slightly and secondarily. This form or forms, Gowers, Stockman and others have called "intramuscular fibrositis."—Ed.)

Fibrositis

Fibrositis is an inflammation of connective tissue. Common sites for fibrositis are in deep fascia, muscle sheaths, subcutaneous tissues and fibrous portion of joint capsules and related ligaments. Classified on anatomic grounds the main forms are panniculitis (fibrositis of subcutaneous tissue), bursal or tenosynovial fibrositis, fascial and intramuscular fibrositis, periarticular fibrositis, and perineural fibrositis.[337, 388, 441] On etiologic grounds it is classified as infectious or toxic, and traumatic (Telling [502]) or as in-

flammatory fibrositis (from infection, toxins, or trauma) and degenerative fibrositis (from tissue age) (Buckley [388]).

Etiology and Pathogenesis. Since inflammatory reactions in fibrous tissue are common to many "rheumatic" and other diseases, some writers, not without a pathologic basis, speak of fibrositis of rheumatic fever, of gout, of gonorrhea and so on (Telling [502]). Forms of fibrositis are undoubtedly part of these diseases, but these are thought of as secondary fibrositis in association with a dominant, recognized clinical syndrome. When writers speak of "fibrositis" they usually mean a primary form—disease of fibrous tissue independent of disease elsewhere. Precipitating factors are given as influenza and respiratory infections, thermal and barometric changes, acute injury or chronic strain. Actual causes are given as general or focal infections, "intestinal toxemia," "metabolic derangements," physical fatigue.[337] In many cases the cause is unknown. Chilling and climatic change are regarded by some [442, 502] as primary causes, but Buckley [388] considered them only precipitants: "Damp and cold will never cause more than passing stiffness in the absence of toxic substances, whether these are bacterial or metabolic in origin."

The pathogenesis of the disease involves an inflammatory exudate which may produce transient symptoms and then resolve. If resolution does not occur, the exudate becomes organized and gives rise to nodules, cords or bands in muscles or large indurated areas with painful tender spots.[337]

Symptoms. The symptoms are pain, stiffness, soreness, tenderness of affected tissues, and sometimes spasm of related muscles. Pain may be continuous or intermittent, sharp or dull. Stiffness and pain are often worse on waking in the morning and after an hour or so of inactivity during the day, but lessen after moderate activity. Such "jelling" is presumably due to the results of capillary congestion that accompanies inactivity and is relieved by some motion.[502] Fibrositis may be diffuse, affecting various anatomic regions, but is usually localized. Local varieties often have separate names as each has its special symptomatology; they are described by Alexander,[337] Buckley,[388] Telling,[502] and Willcox.[441]

Panniculitis may be widespread or localized to thighs or neck. When the neck is affected aching pain occurs in the occipital region and extends over the vertex: "fibrositic or indurative headaches." Telling considered them the commonest type of chronic or intermittent headache, "the four diagnostic features of which are persistency, thickening, nape-of-the-neck location, and tenderness." Pain is variably persistent and intense. Many cases of pleurodynia, fibrositis of the chest, are diagnosed angina pectoris. Certain vague abdominal pains are due to fibrositis of the rectus or other muscles. In abdominal fibrositis pain and tenderness are elicited by "fingertip pressure" rather than by "flat-hand pressure"; tender spots are more or less localized, but may be multiple and occupy positions not usually affected by visceral disease; muscle rigidity (usually present in the latter) is absent, and pain may be intermittent and affected by weather.

Perineural fibrositis generally affects brachial or sciatic nerves and is often called " neuritis," a misnomer unfortunately sanctioned by physicians. In " brachial perineuritis " there is tenderness over the brachial plexus above and below the clavicle and pain when the arm is abducted. Pain follows the distribution of nerves affected. " Brachialgia " may be associated with fibrositis of the subacromial bursa, deltoid muscle, or long head of the biceps. Many cases of sciatica are from perineural fibrositis, which may accompany lumbosacral and sacro-iliac disease and strain. Gluteal fibrositis may be present with or without sciatic fibrositis, as may lumbar fibrositis (lumbago) also. Telling believed there were more cases of fibrositic " trigeminal " neuralgia than of true trigeminal neuralgia.

The two commonest forms of fibrositis are the localized or diffuse intramuscular fibrositis (" myalgia," " neuromuscular pain," " muscular rheumatism "), and periarticular fibrositis (" arthralgia," " capsular rheumatism "). (Without further definition the term " arthralgia " has been used herein by several writers [Gray,[251] Monroe,[296] Dreyer and Reed [331]] who contrasted it with atrophic or hypertrophic arthritis. May one assume that periarticular fibrositis was present?—Ed.) Willcox [441] and Hench [106] emphasized the importance of differentiating the latter from " arthritis " which it is usually erroneously called. Symptoms of periarticular fibrositis are stiffness and soreness of joints, particularly after sleeping or resting, tenderness which is often evanescent, and pain often brought out only when the capsule is stretched. Symptoms are marked by variability and transiency but may be continuous. Differentiation from arthritis rests on persistency with which sedimentation rates, roentgenograms, blood counts, and weight curves are normal and on the general absence of muscle atrophy, deformity, and significant swelling. When " swelling " is present it is usually slight, localized and extra-articular, more of a " thickening " than actual swelling, and hydrops is absent (Hench [106]).

Some writers make much of the nodules of fibrositis which to others seem " only accessible to the finger of faith." Because some consider it difficult to locate nodules or to demonstrate pathologic changes in tissues removed at biopsy, fibrositis has been defined as a " disease which physicians found but surgeons rarely find " (Telling [502]). Fibrositic indurations may be non-nodular (as strands, tracts, sheaths) or nodular. Of the latter there are presumably three kinds: large nodules (generally in fibrous aponeuroses), small nodules (generally in muscle bundles), and " myogeloses." The last are small sharply-localized areas of hardening in muscles, chiefly gluteal, which Lange (1931) and Nicola (1932) ascribed to local chemical disturbances, possibly local accumulations of lactic acid, and which are " negative " on biopsy. The nodular indurations consist presumably of inflammation of the perimyseum and vary in size " from a pea to an almond " (Sutro [503]). Obvious visible nodules are the exception, not the rule as some have led themselves to expect.[502] Cyriax [504] believed that around most of the nodules are small localized muscular contractions, and that when

nodules rapidly "disappear" under various measures, it is the muscular contraction that disappears, leaving a residual nodule too small to palpate.

Pathologic Studies. Such studies have concerned nodules more than other tissues. Nodules consist of "fibrous septa enclosing muscle fibers and bundles of characteristically vague and ill-defined outline," according to Telling [502] who stated that nodules of fibrositis are different in anatomy, pathology, and distribution from the nodular formations of rheumatic fever, which are "still further differentiated by being absolutely painless, even on palpation."

The small or fairly large subcutaneous nodules frequently found in sacro-iliac regions are regarded by many as evidence of fibrositis, active or old. They may be painless or painful depending on the stage of inflammation therein. Because they are often found in patients who give no history of fibrositis, some regard them as of no significance. Among 170 unselected hospital patients with various complaints Sutro [503] found subcutaneous nodules, generally over sacro-iliac joints or near the tips of the lumbar spinous processes, in 94 cases (unilateral in 45, bilateral in 49). Thirty-three of the 170 patients had low backache; 10 had no nodules, and 16 had tender and seven non-tender nodules. Tender nodules were removed in four cases: One patient was a woman with low backache and sacro-iliac arthritis: she claimed complete relief after nodules were removed. One was a patient with subastragalar tuberculosis and no backache. One patient had a low backache and sacro-iliac arthritis; the backache persisted after operation but local tenderness disappeared. One patient had a low backache, sacro-iliac arthritis and no postoperative relief. Examination of the nodules in these four cases showed them to consist of lobules of adult fat of normal appearance without signs of recent or old inflammation or other evidence of metabolic or toxic disturbance. Sutro concluded that they were "protective buffer-pads over poorly muscle-covered areas of sacrum and ilium," that they were not part of any recognized disease and may be found in apparently normal persons, and that they were wholly different from those of rheumatic fever, atrophic arthritis, and syphilis.

(This study represents a laudable beginning but does not settle the issue. The relief which two of the four patients obtained by removal of nodules is not explained, nor is the tenderness of the nodules. Many more nodules in various stages of tenderness and formation should be examined, as well as sections of adjacent fibrous tissue. It is difficult to believe that such nodules are "normal" even if they are often symptomless and in patients who give no history of fibrositis.—Ed.)

Laboratory Data. Of 68 patients, 36 per cent had an abnormal levulose tolerance test.[291] In five cases the average values for albumin, globulin and total protein of blood were a little below normal.[257] Blood groups were normally distributed.[260]

Treatment. This follows the same general principles as in atrophic arthritis. Removal of foci is advised.[388, 502] Vaccines seemed valueless to some,[388] helpful to others.[106] Buckley [388] considered protein therapy useful,

and for empiric reasons advised the use of onions and garlic in diet. In some cases the affected part must be rested with slings and strapping, but rest is not indicated for fibrositis of neck and chest, according to Telling.[502] Various forms of physical therapy were employed[337]: short wave diathermy,[17, 18, 356, 505] Fango,[352] histamine ionization,[17, 329, 388] paraffin baths, pelvic diathermy[506] and fever therapy.[48, 74] "The only curative therapy" is massage, according to many.[254, 502] Massage should be light over affected tissues, except nodules "which can be rubbed away."[388] Tender nodules were surgically removed by Stockman.[507] For associated fatigue, glycine (amino acetic acid) has been tried with variable results.[508]

Epidemic Myalgia. Carney[509] saw 87 cases of epidemic pleurodynia in one month in West Virginia. Typical symptoms were fever, rapid pulse and respiration, pain at the attachment of the diaphragm to the anterior abdominal wall, or at times in the epigastrium. Pain was greatly aggravated by respiration. The disease usually ended in about 24 hours. A plasmodium was suspected.

Noting the frequency with which persons suddenly developed one-sided "stiff neck," Massell and Solomon[510] questioned 61 patients and 52 hospital colleagues who had recently suffered therewith. Symptoms were usually noted on waking, were occasionally gone by noon, generally lasted one to two days subacutely, and in some cases hung on mildly for several days or weeks. Sites of maximal pain in order of frequency were: the origin of the trapezius muscle at the superior nuchal line; half way down the neck along the border of the trapezius; at the insertion of the sternocleidomastoid muscle; and at the lower border of the trapezius at the shoulder. No nodules were felt. Heat gave relief; massage was painful but gave more relief. Treated patients had the condition as long as the others, however. A hypothetical "twist of the neck while asleep" or "exposure to draft" did not seem as likely a cause as an epidemic infection, suspected but not investigated. The attitude of physicians to "epidemic benign myalgia" should not be the same as that of patients—one of annoyed tolerance and resignation.

(The inquiry, being mostly of the questionnaire type, did not escape the inadequacies inherent therein.—Ed.)

Myositis Ossificans. Three types were mentioned: (1) progressiva, (2) circumscripta, (3) post-traumatic. Studies on a patient with the progressive type convinced Wilkins and his colleagues[511] that phosphatase is intimately associated with the ossification. At various stages of the disease biopsies were made on normal and affected tissues. Serum calcium, plasma phosphatase, and inorganic phosphorus were normal. Total and inorganic phosphorus of diseased muscle was much lower than in normal muscle. The phosphatase activity of affected muscle in the pre-ossification stage was 800 to 1,600 times that of normal muscle, and several times that of normal bone; that of heterotopic bone was much higher than that of normal bone.

Features of a case of traumatic myositis ossificans, reported by Taylor, Shea and Argyr [512] included contusion, swelling, induration, limitation, tenderness and palpation of a hard mass which could be rotated around the bone shaft. Serial roentgenograms reveal a mass of increasing density separated from the bone shaft. As density increased the mass showed lamellae corresponding to ossification of muscle bundles or fascial layers. Osteogenic sarcoma is differentiated from myositis ossificans in that the former progresses instead of regressing after four to six weeks, is usually near the epiphysis, and becomes connected with the bone. Treatment of traumatic myositis ossificans includes rest, heat to promote absorption of the hematoma, and excision if function is disturbed.

Chronic Generalized Fibromyositis (Progressive Myositis Fibrosa). Few cases have been reported. In one case recorded by Ornsteen [501] hardness and stiffness of muscles of limbs, back and abdomen, severe muscle spasms, myotonia, sweats, rapid respiration and pulse, and loss of weight of one year's duration were present. Creatinuria was absent. Biopsy of muscle showed a marked increase in subcutaneous fibrous tissue and severe scattered degenerative changes in many muscle cells. "Absence of skin lesions differentiated it from dermatomyositis." The differential diagnosis and a review of reported cases were discussed.

Dermatomyositis. This was the suggested diagnosis in a case seen by McAlpine.[513] Pain behind the knees, and later diffuse swelling of legs, hands and forearms were present. These subsided and progressive stiffness and weakness of the hands ensued. Muscles of the hands, forearms, and legs and the rectus muscle were hard. Leukocytes numbered 14,500 to 18,000 per cu. mm. blood, eosinophiles comprising 33 to 37 per cent. Biopsy revealed increases in sheath nuclei but no giant nuclei, Trichinella or marked inflammatory infiltration.

Miscellaneous Myopathies. Features of myasthenia gravis and various muscular atrophies were reviewed by Aring and Cobb.[514] Myopathies can be separated into two groups, according to Milhorat and Wolff [515]: (1) those in which creatinuria is marked and creatine tolerance grossly deficient, a deficiency exaggerated by the administration of glycocoll, and (2) those in which creatinuria is slight and the creatine tolerance is slightly deficient and not exaggerated with glycocoll.

Traumatic Injuries to Muscles and Tendons. Clinical features and differentiation of various traumatic lesions were described by Haldeman and Soto-Hall.[516] Symptoms common to most ruptures were sudden sharp pain or "snap" during violent effort, inability thereafter to perform certain motions, and the appearance of ecchymoses and a defect in muscle or tendon. A lightly-exposed roentgenogram may show a defect in muscle shadow or a chip of bone torn from a tendon insertion. Application of faradic currents to a ruptured muscle causes it to contract with pain at the site of tear. Injections of procaine hydrochloride into the subdeltoid bursa helped to dif-

ferentiate between bursitis with reflex spasm of the supraspinatus muscle, and tears of the supraspinatus tendon. If the former is present the arm can be abducted actively and painlessly a few minutes after injection; if the latter is present active abduction is not improved. In the lower extremity the quadriceps, and in the upper the supraspinatus, muscle or tendon is most likely to be torn; especially in the supraspinatus muscle, degenerative changes of advancing age (fibrillation or fraying, even perforation of the supraspinatus tendon into the joint) play a predisposing rôle.

Subdeltoid Bursitis. This results from trauma more often than from allergic, toxic or infectious agents, in Polmer's [517] experience. Diathermy was most helpful if small rounded electrodes were used and properly placed. Rest and ultraviolet irradiation were also used. Of 65 patients, 32 were men, 33 women; the age incidence was 25 to 71 years. Forty-seven patients who were relieved received an average of 16 treatments. Patients with calcified subdeltoid bursitis (post-traumatic?) were frequently notably relieved when Haldeman and Soto-Hall [516] injected 10 to 15 c.c. of 1 per cent procaine hydrochloride into the bursa. Calcium deposits sometimes disappeared within a few days. Often no other treatment was necessary. Injections were sometimes repeated. (Such calcium deposits sometimes rapidly disappear spontaneously.—Ed.) Others advocated short wave therapy,[18, 78, 80] histamine iontophoresis,[17, 329] massage and manipulation.[340]

Miscellaneous Conditions

Bunions. Bunions may seem of minor importance, but they are painful, crippling, deforming and unsightly. Stanley and Breck [518] operated on 211 bunions (129 patients) by the Petersen-Fowler-Singley procedure: a web-incision between the great and second toes. After backward and mesial disarticulation of the great toe the exostosis was removed with "uniformly good results." In 20 years' experience no patient needed a second operation or complained of a poor result. (They were California State prisoners.—Ed.) The operation had these advantages: the technic is simple and trauma slight; the scar is not exposed to subsequent trauma from shoes; the weight-bearing buttress of the joint is undisturbed; the period of disability is minimized and danger of ankylosis is negligible.

Osteopoikilosis (*Bone Speckles*). This represents an asymptomatic familial anomaly of bone discovered accidentally in roentgenograms. Small circumscribed areas of increased density (2 to 5 cm. in length) may appear almost anywhere in the skeleton. In some cases dark vertical striations giving shadows much denser (less opaque) than normal bone are seen. Sutherland [519] reviewed the 32 reported cases and discussed the relation of osteopoikilosis to melorheostosis and chondrodysplasia. (An additional case was presented, that of a young man with multiple areas of circumscribed mottling in many bones. Linear striations [10 mm. long, 5 mm. wide] were also seen in diaphyses of tibia and fibula. Blood calcium, phosphorus and phosphatase were normal. His mother and a brother were similarly affected.—Ed.)

Multiple Myeloma. Cases of myelomatosis may present features resembling hyperparathyroidism. Such a case was seen by Enzer and Lieberman.[520] An elderly man developed low backache and lost 30 pounds (13.6 kg.). Marked emaciation, a tender lumbar spine and sacro-iliac joints, and Heberden's nodes were noted. Roentgenograms revealed multiple areas of bone destruction in spine, pelvis and femurs, and (unrelated) hypertrophic arthritis. Bence-Jones albumose was not found (one test). Blood calcium was 11.8 to 13.7 mg. and phosphorus 3.2 mg. per 100 c.c. A negative calcium balance was present (in the diet 200 mg., in urine 530 mg.). Hyperparathyroidism was suspected, but at operation no tumor was found. Postoperative pneumonia was fatal. Necropsy revealed myelomatosis and marked parathyroid atrophy (presumably from functional hyperparathyroidism).

Differentiation. Cases of hyperparathyroidism generally have an elevated serum and urinary calcium, a normal or low serum phosphorus. Sometimes serum calcium is normal. In myelomatosis hypercalcemia may also appear, but serum phosphorus is generally normal or high. Serum phosphatase is generally high in hyperparathyroidism, normal with myeloma. Bence-Jones albumose is not always present in myelomatosis and may be present in other diseases (including hyperparathyroidism[479]). A negative calcium balance may be present in both. Differentiation, therefore, may be difficult and should be made only after comprehensive, and not superficial, clinical, chemical, radiologic and metabolic studies, with biopsy if necessary.

Physiology of Articular Tissues

Collins[273] found that, in general, the chemistry of synovial fluid is the same as that of the patient's blood. Differences in sugar and protein concentrations may be found. Synovial fluid sugar is apt to be much lower than blood sugar in cases with infected synovial fluid but not in those in which fluid is sterile even though it has a high cell count. Thus a synovial sugar of 50 mg. or more below the blood sugar level is strong evidence of bacterial invasion of the fluid. Total proteins are increased in most effusions, especially with many cells. Consistent increases in protein and cell count in fluid in atrophic arthritis indicate an exudate, not a transudate, is present. Studies on synovial cytology were more helpful than those of synovial chemistry. Six types of cells are commonly found: polymorphonuclears, eosinophiles, lymphocytes, monocytes, macrocytes (large phagocytic cells) and synovial lining cells. The total cell count and percentage of polymorphonuclear cells vary in different diseases (table 2). Whereas the normal synovial fluid contains " about 200 cells " per cu. mm. of which less than 10 per cent are polymorphonuclears, joint fluid in atrophic arthritis contains 5,000 to 60,000 nucleated cells, of which generally 70 to 90 per cent are polymorphonuclears. Total and differential counts were much lower in hypertrophic than in atrophic arthritis, and only slightly altered in intermittent hydrops and in " sympathetic joint effusions "—with inflammatory lesions near but not in joints. (Collins' more extensive data have since appeared.[521]—Ed.)

TABLE II

Studies on Synovial Cytology (Collins[273])

Condition	Cases studied	Total nucleated cells, per cu. mm. synovial fluid		Polymorphonuclear leukocytes, per cent	
		Usually	Range	Usually	Range
Normal		"About 200"		Below 10	
Atrophic arthritis	35	10,000–20,000	5,000–60,000	70–90	40–100
Hypertrophic arthritis	4	Below 1,000	Below 1,000–10,000	Below 10	0–20
Gonorrheal arthritis (sterile fluids)	4		5,000–30,000		30–80
Intermittent hydrops	1 (two samples)		1,600; 2,500		58, 78
"Sympathetic joint effusion"	2		Below 1,000		0–20

Warren, Bennett and Bauer[522] studied the synovial fluid at necropsy of 150 persons who had died of miscellaneous conditions and had had no joint symptoms. Synovial cytology may be unaltered, though the patient has a marked leukocytosis. Cartilage defects and débris may increase the nucleated cells and percentage of phagocytes. The total nucleated cell count per cu. mm. is reduced in synovial effusions in edematous patients. Patients dying with any severe infection (without joint symptoms) sometimes have a high, synovial total cell count and polymorphonuclear leukocytosis.

Leukocytes contain proteolytic (tryptic) ferments which, in sufficient amounts, can destroy articular cartilage. To prevent leukocytes in synovial fluid from doing this, synovial fluid contains antitryptic substances which inhibit tryptic digestion (Holmes, Keefer, Myers[523, 524]). These antitryptic substances (which can be removed from synovial fluid by extraction with chloroform) probably come from blood plasma, as their concentrations in fluid and plasma are similar. Synovia cannot protect cartilage adequately when its antitryptic powers are reduced in the presence of effusions containing large numbers of cells, especially polymorphonuclears, for from such effusions, particularly purulent exudates, proteolytic enzymes are liberated in great amounts. (Hence the necessity of draining purulent or suspected purulent effusions promptly to prevent or minimize cartilage destruction.—Ed.) Nevertheless, synovial fluid is apparently able to prevent or inhibit cartilage destruction even when the synovial fluid contains as many as 20,000 leukocytes per cu. mm., for it was found that although cartilage destruction occurred in vitro in the presence of synovial fluid in two cases of staphylococcic arthritis in which synovial fluid cells numbered 110,000 to 240,000 per cu. mm., car-

tilage destruction did not occur in the presence of synovia in seven cases of gonorrheal arthritis with 7,850 to 21,000 cells per cu. mm. of synovia, or in three cases of tuberculous arthritis with synovial counts of from 6,500 to 11,600 cells.

To study healing processes in joints, Bennett and Bauer [525] compared the processes of cartilage repair in adult dogs to those in young dogs in which epiphyseal union had not yet occurred. Defects of central, non-weight bearing articular cartilage were produced surgically. Repair of these defects was no more rapid or complete in young dogs than in adult dogs. In both, healing was slow: none was noted after four to 12 weeks; it was notably present but incomplete after 20 to 28 weeks. Repair occurred in three ways: (1) an independent proliferation of original cartilage cells; this was greater in the deeper zones of articular cartilage than in the more superficial zones, (2) proliferation of vascular tissue from perichondral margins, (3) when subchondral marrow spaces were involved in the surgical defect there was also an ingrowth of vascular connective tissue therefrom. Repair (active proliferation of cartilage cells) occurred most satisfactorily when the defect extended into subchondral bone (in which case granulation tissue from marrow spaces gradually filled the defect), or in crevices where cartilage was protected from friction. The latter would indicate that function may inhibit repair. Bennett and Bauer were unable to corroborate the opinion of Key (1931) that such defects in articular cartilage may be an important cause of intra-articular disease. Associated intra-articular disease was found only in joints where patellae became displaced.

Studies on the comparative value of four dyes used for the arthrographic diagnosis of joint mice, cysts, semilunar injury and so forth, were made by Keller.[526] For diagnostic purposes the ideal dye should produce sufficient opacity for roentgenographic detail, a minimum of discomfort and reaction after injection, and be eliminated rapidly enough to avoid irritation as a foreign substance but not too rapidly to prevent painstaking radiologic studies. All four dyes used produced satisfactory opacity, but hippuran gave the mildest post-injection reaction, a sense of fullness without pain, and it was therefore preferred. It disappeared from joints in three to four hours. After administration of arthropsin articular pain lasted a few hours (time unstated), after neoiopax three to 10 days; after skiodan it was severe and lasted over two weeks. Some patients with "chronic arthritis" noted improvement in the injected joint after the post-injection reactions. Therefore if one wishes to attempt a therapeutic as well as diagnostic procedure, arthropsin was recommended. It disappears from normal joints in 17 to 24 hours, sooner from joints subacutely inflamed, much slower from joints with thickened capsules. Use of these dyes is presumably contraindicated for patients with liver or kidney disease or hyperthyroidism. Arthropsin contains 68 per cent iodine, and is a 10 per cent solution of the disodium salt of tetraiodo-ortho-sulpho-benzoate.

The Golgi apparatus appears as reticular material in almost every cell of all animals. Its nature is uncertain. Some consider it an artefact, but it has been observed in living cells. Others regard it as indicating an area of protoplasm which is the site of special activities. Whatever it is, this "apparatus" is a morphologic component of cells demonstrable in certain circumstances and altered by environmental changes that affect other parts of the cell only slightly or slowly. Thus when tissues are removed from the body the Golgi material disappears before there are any (other) visible autolytic changes. In mild degenerative conditions in which the blood supply is impaired or disintegrative changes are present in cells the Golgi apparatus is grossly altered or absent. Never noted previously, a well-developed Golgi apparatus comparable with that of other connective tissue cells was demonstrated by King [527] in synovial tissues of humans, horses and dogs. The apparatus becomes enlarged in conditions with increased synovial fluid. Cells, including synovial cells, free in synovial fluid also show the apparatus. Since it is not demonstrable in degenerative states, its well-developed character in synovial cells indicated to King that synovia is not a product of degeneration as some contend. Since the Golgi bodies of synovial cells are enlarged in inflammatory conditions he suggested that the enlarged apparatuses indicate secretory activity of synovial cells. (A good review of synovial histology was given.—Ed.)

Allen [528] noted that non-particulate solutions (methylene blue and trypan blue) escaped from knee joints of live cats and appeared in iliac lymph nodes in one to four minutes, but that particulate matter (India ink, erythrocytes) did not appear in nodes for three to five hours. Experiments were then done on perfused kittens just after death. Muscular contraction, joint involvement and increased joint tension caused more rapid passage of fluid and particulate matter from joints to lymphatics. Certain bacteria were injected directly into joints and subsequent cultures of blood and lymph nodes were taken. Animals allowed to move around had a tendency to show more positive blood cultures than those whose joints were fixed in plaster. Allen interpreted these results as evidence that immobilization of infected joints is desirable to prevent spread of infection.

A method for measuring and recording joint function was reported by Cave and Roberts,[529] and Moore [530] described an apparatus for articulometry of feet.

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The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1936–1937) articles which will greatly facilitate the preparation of subsequent reviews.

CASE REPORTS

EXTRAPYRAMIDAL SYNDROME AND ENCEPHALOGRAPHIC PICTURE OF PROGRESSIVE INTERNAL HYDROCEPHALUS IN CHRONIC HYPOGLYCEMIA *

By Abram Blau, M.D., *New York, N. Y.*, Norman Reider, M.D., *Topeka, Kansas,* and Morris B. Bender, M.D., *New York, N. Y.*

In the past decade since the description of the syndrome of spontaneous hypoglycemia or hyperinsulinism, numerous cases have been recognized and reported. The variegated symptom-complex has become more definitely delineated and a number of comprehensive reviews of the subject have appeared.[1] The neuropsychiatric symptoms of hypoglycemia are among the most interesting, and have received special attention by Stone [2] and others.

The purpose of this communication is to record a case of chronic spontaneous hypoglycemia which has been studied over a period of 16 months of hospitalization. The outstanding features included convulsive seizures, hypoglycemia, and a persistent extrapyramidal syndrome with encephalographic evidence of progressive internal hydrocephalus.

Case Report

History. H. L., a white male, aged 49 years, was admitted in a comatose condition to the Neurological Service of the Mount Sinai Hospital on February 16, 1934.

The familial and past history were essentially negative. He had followed various forms of employment, including that of a painter for a short period, until June 1933, when he began to suffer from weakness, tiredness, mental depression, and attacks of dizziness. One month later, he began to have periods of unconsciousness accompanied by abnormal movements and rigidities in the extremities. During these episodes his breathing became noisy and saliva drooled from his mouth. The entire attack lasted from one to three hours; recovery was spontaneous. On regaining consciousness he complained of headache and was unable to recall any of the preceding events. There was no aura, he did not cry out at any time, did not bite his tongue, nor was there incontinence. These episodes recurred at intervals of about a month, and were not noted to occur at any particular time of the day. During the eight months preceding his present admission his speech became slower and thicker, he seemed to have difficulties in articulation, his vision and hearing became impaired, and micturition became more frequent, without polydypsia. A change in his personality was noted by his friends and relatives; he became morose, depressed, asocial, preoccupied, disinterested in his surroundings and definitely detached from his former activities.

On two occasions he was admitted to the neurologic service of another institution (October 22 to November 14, 1933, and from January 12 to February 13, 1934), where a cerebral neoplasm was suspected, but no definite diagnosis could be made. An encephalogram on each admission showed mild cerebral atrophy but failed to show deformity or displacement of the ventricular system. Two blood sugar esti-

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From the Neurological Service of Dr. Israel Strauss, Mount Sinai Hospital, New York, New York.

mations were reported as 189 mg. per cent and 42 mg. per cent respectively. Other clinical and laboratory studies were essentially normal.

Examination showed a well developed and well nourished adult white male in a semi-stuporous condition. The systemic examination was essentially negative. The blood pressure was 140 systolic and 90 diastolic. The positive neurologic signs included hyperactive deep tendon reflexes which were more marked on the left; absent superficial reflexes; Hoffman reflex positive on the left and inconstant on the right; Babinski sign positive on the right and equivocal on the left; and a slight weakness of the left lower facial musculature. The pupils were equal and reacted promptly to light. The fundi oculi were normal. A lumbar puncture revealed clear fluid under a pressure of 120 mm. of water. The Queckenstedt test was negative. After the removal of 10 c.c. of fluid the pressure dropped to 40 mm. The stupor persisted and irregular convulsive movements appeared. Fifty c.c. of 50 per cent dextrose were then administered intravenously, without effect. The convulsive movements and stupor continued for another three hours, when he gradually began to respond. The following morning (12 hours later) he was mentally clear.

The diagnoses considered on admission were brain tumor, presenile dementia (Alzheimer's disease), or subacute encephalitis. On April 2, 1934, to rule out a brain tumor, an encephalogram was performed, following which he became stuporous and showed a recurrence of the convulsive semi-purposeful movements. A blood sugar estimation at this time was 45 mg. per cent. Following the intravenous administration of 70 c.c. of 50 per cent glucose, he regained consciousness, responded to questions and began to complain of headache. The diagnosis of hypoglycemia became probable and was confirmed by the subsequent course.

The course and data are best presented under separate headings:

(*a*) *Hypoglycemic Seizures.* The hypoglycemic seizures were the outstanding manifestations of the illness. During a period of 14 months, 130 seizures were observed (table 1). The seizures occurred at all times of the day, but a majority were in the afternoon.

TABLE I

The distribution and frequency of the attacks are tabulated. During July, the patient was receiving foreign protein fever therapy. The lower part of the table shows the greater frequency of the attacks during the afternoon.

Month	*Number of Attacks*
April 1934	7
May	19
June	26
July	0
August	6
September	8
October	16
November	4
December	10
January 1935	8
February	8
March	8
April	6
May	4
Total number of attacks	130

Period of Day	*Number of Attacks*
12 m. to 6 a.m.	10
6 a.m. to 12 Noon	18
Noon to 6 p.m.	77
6 p.m. to 12 Noon	25

A seizure was preceded by apprehensiveness and irritability; the patient expressed ideas of hopelessness, said that he was going to die and became very uncoöperative. He then became drowsy and stupor gradually supervened. The breathing became stertorous and noisy and bizarre convulsive movements set in. The movements were clonic and had a semi-purposeful character: these were groping of the hands, thrashing of the arms, treading motions of the legs, and turning movements of the body. The movements were irregular, involving either the whole body, one side, or even single limbs, but at no time was there a cortical spread of the seizure. The eyes were closed and the mouth drooped, and sometimes the head would roll from side to side. There were no clonic movements of the jaw, or biting of the tongue or lips. There was a marked increase of salivation but as a rule no frothing at the mouth. As the attack continued considerable amounts of saliva would drool from the mouth, and on one occasion 250 c.c. of saliva were collected within a period of one and one-half hours. Unconsciousness was complete, but the pupils continued to react to light. The tendon reflexes were usually hyperactive, and occasionally showed some inequality. A Babinski sign was frequently elicited, but this was inconstant and varied from side to side.

At times, particularly in the later period of observation, "minor" attacks without convulsive movements would occur. These were characterized by lapses in which he would become drowsy, restless, and would assume a vacant expression and blink his eyelids. His responses were automatic, and no mental contact could be made. These attacks would last from a few minutes to one-half hour.

If not ended by an intravenous injection of glucose, the "major" attacks continued for two to three hours. He would then recover spontaneously without the ingestion or injection of any nutriment. Following these spells he was completely amnesic for the events occurring during or immediately preceding the seizure. The attack could always be aborted immediately by the intravenous injection of dextrose. He was usually given 50 c.c. of 50 per cent dextrose intravenously, but relief could be obtained with as little as 5 c.c. of 50 per cent dextrose. Figure 1 *C* shows the effect on the blood sugar of intravenous glucose administered to relieve two hypoglycemic seizures. Normal saline intravenously in similar amounts had no effect. Sweetened orange juice by mouth usually prevented an attack when given at the time when restlessness appeared, but administered through a stomach tube when the patient was unconscious, caused but little response. Hypodermoclysis or proctoclysis of 5 per cent glucose was no more effective than glucose by mouth. Epinephrine (1 c.c.), pituitrin (1 c.c.), and Collip's diabetogenic pituitary extract,* [3] as well as many other glandular preparations were ineffective in relieving an attack.

Blood sugar estimations (total reducing substance) during seizures were as low as 30 mg. per cent. However, a low blood sugar was not invariably associated with a hypoglycemic attack. The correlation between the blood sugar and the condition of the patient is shown by figures 1 *A*, *B* and *C*.

During the hypoglycemic seizure the blood pressure usually increased slightly but at times decreased; the secretion of saliva increased, the ocular tension (by quantitative measure) decreased, and the blood cholesterol was decreased. The electrocardiogram showed minor changes as inversion of the T_1 and T_2 waves, and sinus tachycardia.

An attack could not be precipitated by 10 units of insulin administered subcutaneously about one hour after recovery from a seizure. Induced alkalosis by hyperpnea for three minutes was followed by a long period of apnea but no other changes. An attack was invariably induced by starving, particularly by eliminating

* This extract, which will raise the blood sugar in a Houssay dog, was kindly furnished expressly for clinical trial on this patient by Dr. J. B. Collip of McGill University, Montreal, Canada.

breakfast, and often by the omission of the sweetened orange juice which he was taking every two hours.

(*b*) *Neuropsychiatric Symptomatology.* The course was marked by the progressive and permanent establishment of extrapyramidal and cortical signs. His stance became stooped, slouching, and more and more like that of a Parkinsonian. The gait was slow and stiff with a gradual diminution and finally a complete loss of associative movements of the arms. He later showed retropulsive tendencies. His hands became tremulous and a perioral tremor developed. The tremor of the fingers

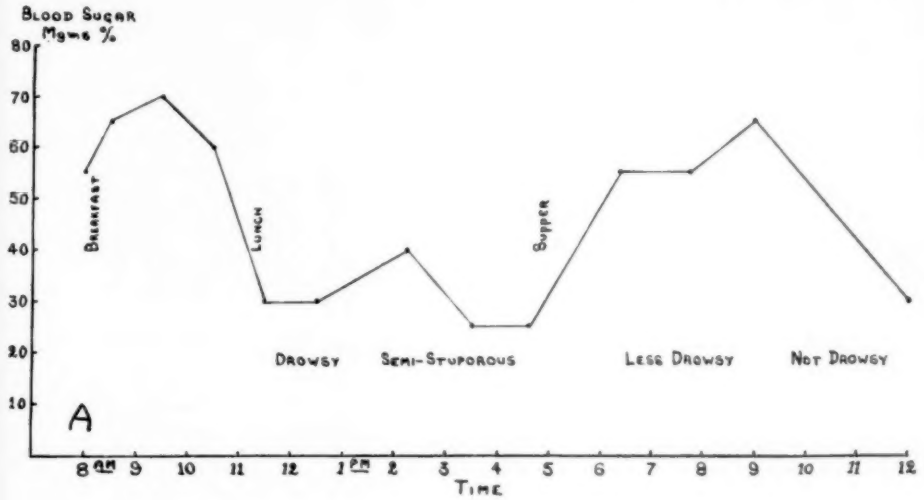

Fig. 1 *A*.

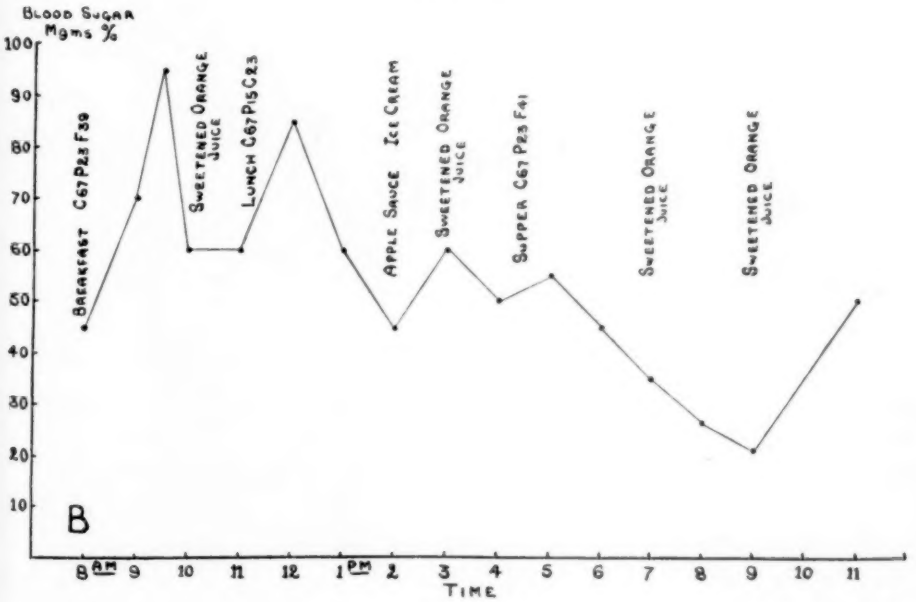

Fig. 1 *B*.

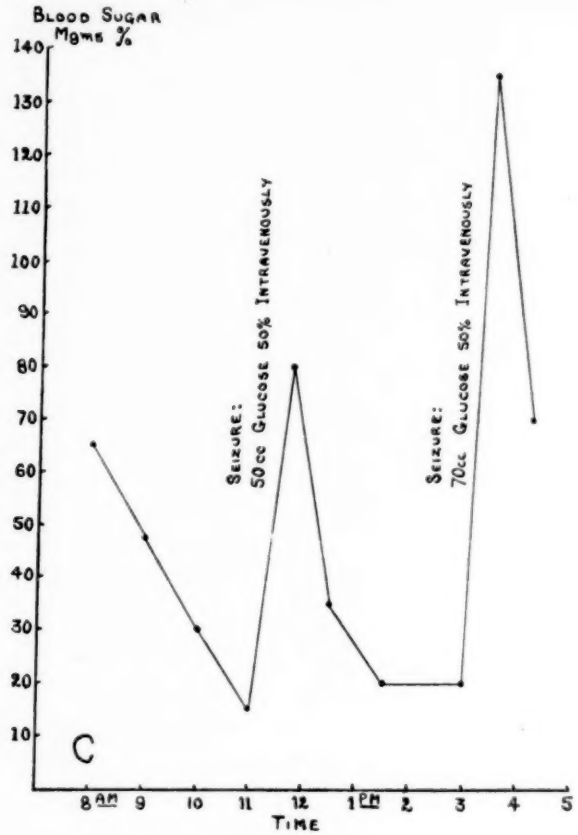

Fig. 1 *C*.

FIG. 1 *A*, *B* AND *C*. Graphs of blood sugar values estimated at frequent intervals throughout the day. There was no strict parallelism between the blood sugar values and the symptoms of hypoglycemia. Intravenous glucose was followed by a sharp rise and fall of the blood sugar.

was coarse and arrhythmic. On the finger to nose test he showed a slight intention tremor. Bilateral adiadochokinesis was noted early in his course. From day to day the speech became more and more dysarthric, thick, slow, syllabic, whining and, especially preceding an attack, was unintelligible.

The cranial nerves, except for hearing, were not involved. The fundi showed no changes, and repeated visual field examinations were normal. Visual acuity was O.D. 20/30, O.S. 20/70. The pupils were equal, regular and reacted well to light and accommodation. No weakness of the external ocular muscles was noted. Two months after admission, the patient complained of impaired hearing in the right ear, and this progressed to involve both sides. The hearing defect was found to be of the nerve type. The levels of both the upper and lower tones were markedly diminished, the upper tones being more involved. The deafness was more marked in the right ear. Immediately preceding discharge from the hospital he could not hear the tick of a watch placed 1 cm. from the ear, when it was heard by the examiner at two feet; when placed against the ear, it was audible. Vestibular function as tested by the response to caloric (cold) stimulation, was normal.

The motor power became progressively weaker. The muscles showed increased myotatic irritability. During several hypoglycemic attacks coarse fibrillations were noted in the right forearm. The tendon reflexes were generally hyperactive, and showed inconsistent variations from day to day. Definite pathological reflexes, as the Babinski sign and other confirmatories were noted from time to time varying from side to side, but these were not persistent.

Sensation was not affected except for a short period four months after admission. At that time he began to complain of paresthesias in his hands and feet, and these gradually involved the forearms and legs. On examination he showed sensory diminution of all modalities in typical glove and stocking distribution. Within three months these signs and symptoms disappeared spontaneously. Apparently there was a transient attack of symmetrical peripheral neuritis.

The *mental condition* was one of progressive intellectual and emotional deterioration. He was completely amnesic regarding the seizures and on recovery from each often showed a short period of confusion. For two weeks in the early period of his observation he showed delusions of persecution and ideas of reference. He thought that the nurse wanted to poison him, that people were taking pictures of him, and he openly accused a number of other patients on the ward. He did not elaborate on these ideas and was irritable and belligerent. He later regained partial insight and reluctantly admitted that it was a product of his imagination.

His interests were minimal and gradually became fewer. He was content to sit by himself, and made few contacts with the other patients. He soon became incapable of coherent speech and his verbal productions were limited to a few requests regarding his immediate needs. When conversation was attempted he used few words and was often simply monosyllabic. When clear he was cognizant of his illness. He knew that he had low blood sugar and frequently reminded the nurses that his orange juice was due. He realized that he was permanently handicapped and that he would be unable to earn a living, so that his general attitude was pessimistic, although he frequently appeared euphoric. At times he was facetious in a simple way and smiled even in irrelevant situations. At other times he became depressed, emotionally unstable, and expressed fears that he would never be healthy. As previously stated, an hypoglycemic attack was preceded by anxiety, apprehensiveness and irritability. His intellectual capacities showed progressive diminution. His memory became impaired both for recent and remote events. As a rule he had good insight into his somatic condition but not regarding his mental defects. His judgment was impaired.

(*c*) *Systemic and Laboratory.* The systemic examination showed no unusual changes except for an increase in weight. On admission he weighed 152 pounds and a year later he had gained 21 pounds. The blood pressure varied from 130 mm. of Hg systolic and 90 diastolic to 160 systolic and 100 diastolic. The numerous laboratory investigations showed very little of significance except those referable to sugar metabolism. The urine was normal and never showed any sugar. Special tests for lead in the urine were negative. The hematologic examination was normal. The cerebrospinal fluid sugar was 15 mg. per cent. The blood cholesterol during an attack was decreased to 105 mg. per cent. The Rehfuss gastric analysis showed a good acid curve with levels of total acid of 58 and of free HCl of 42; no blood or other abnormalities were noted. The stools were normal. The galactose tolerance test for liver function was normal and no sugar was excreted in the urine. Glycogen storage was deficient as there was no notable increase in blood sugar to epinephrine. The basal metabolic rate was plus 6 per cent. An electrocardiogram showed regular sinus rhythm, left ventricular predominance, and an inverted T_2 wave. During an attack the electrocardiogram showed sinus tachycardia and inverted T_1 and T_2 waves. The roentgen-ray of the skull, and a gastrointestinal series were negative.

(*d*) *Blood Sugar.* The Folin-Wu method modified for the estimation of low values was used for the venous blood sugar determinations. The fasting blood sugar

varied from 30 to 45 mg. per cent. On two occasions, when allowance was made for the non-glucose reducing substances in the blood (estimation following yeast fermentation of glucose as compared to a non-fermented specimen), the fasting sugar values were 5 and 7 mg. per cent respectively. These low sugar values as previously stated were not invariably associated with hypoglycemic seizures.

The Janney sugar tolerance test was performed 10 times during the period of observation (figure 2). As shown in the graph, the blood sugar level continued to rise for the first hour, rested at this level for about one hour, and then dropped to a point lower than the original fasting level. During the plateau-like period of high blood sugar value, a trace to 1.4 per cent sugar was noted in the urine on several occasions. Figure 1 *A* and *B* illustrate the diurnal course of the blood sugar while on a regular diet with additional glucose in the form of orange juice. Note that the values of blood sugar decrease in spite of the ingestion of food. Epinephrine and

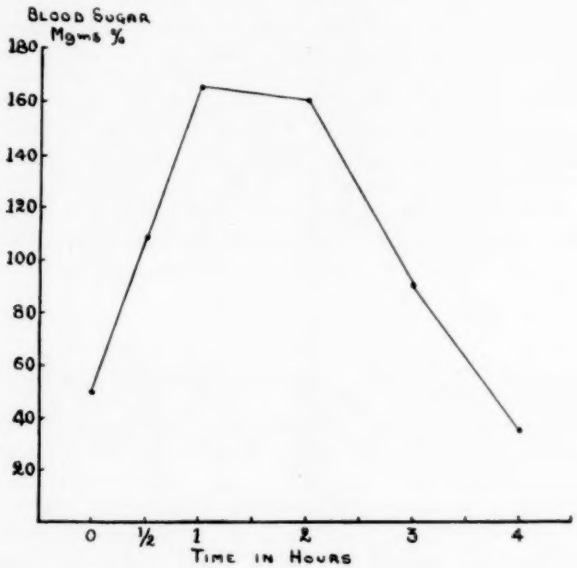

Fig. 2. Blood sugar tolerance curve (from average values of ten tests).

antuitrin tolerance tests demonstrated no significant alteration of the fasting blood sugar curves.

(*e*) *Encephalogram.* Several encephalographic studies were carried out and these showed progressive cerebral pathology. The first encephalogram (figure 3) on April 2, 1934 was reported as: "Both lateral ventricles symmetrical, moderately dilated and in the midline. In the posterior horn there is a shadow which protrudes into the ventricular region which I believe is not pathological. The third ventricle is dilated and in the midline. The iter and fourth ventricle are also slightly dilated. The basilar cisternae are somewhat enlarged, and on some of the films there is evidence of air in the subtentorial region. Subarachnoid markings are not evident." This encephalogram was essentially similar to two others obtained previously one and four months respectively at the other institution. The encephalogram was repeated on March 29, 1935, and the principal change was an increase in the size of the ventricles (figure 4) indicating *progressive internal hydrocephalus.*

(*f*) *Treatment.* Both as a diagnostic and therapeutic measure, an exploratory laparotomy was performed on May 12, 1934, by Dr. A. A. Berg. The pancreas,

adrenals and liver were examined and were found to be normal. Biopsy specimens were removed from the liver and pancreas, and histological examination showed no unusual features.

A great variety of other therapeutic measures was investigated. Since none of these seemed to have any appreciable effect on his condition, they are only mentioned.

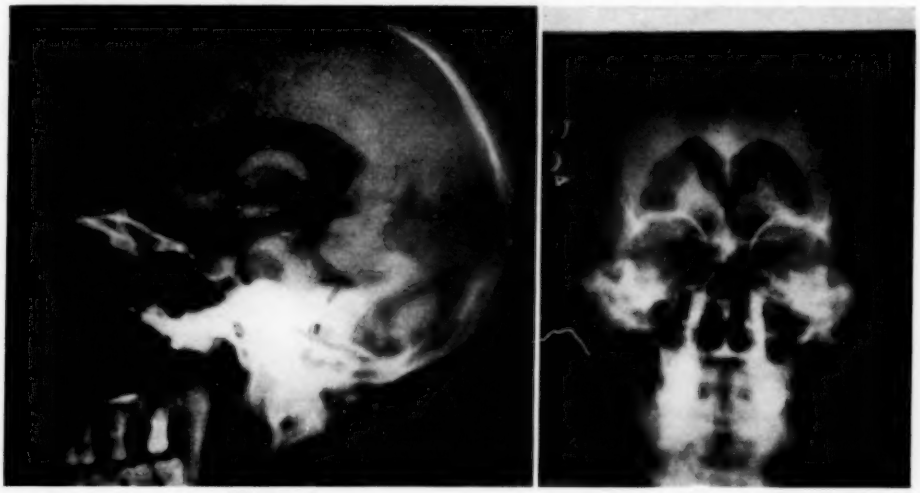

Fig. 3 *A*. Fig. 3 *B*.

FIG. 3 *A* AND *B*. Encephalogram on April 2, 1934, showing internal hydrocephalus.

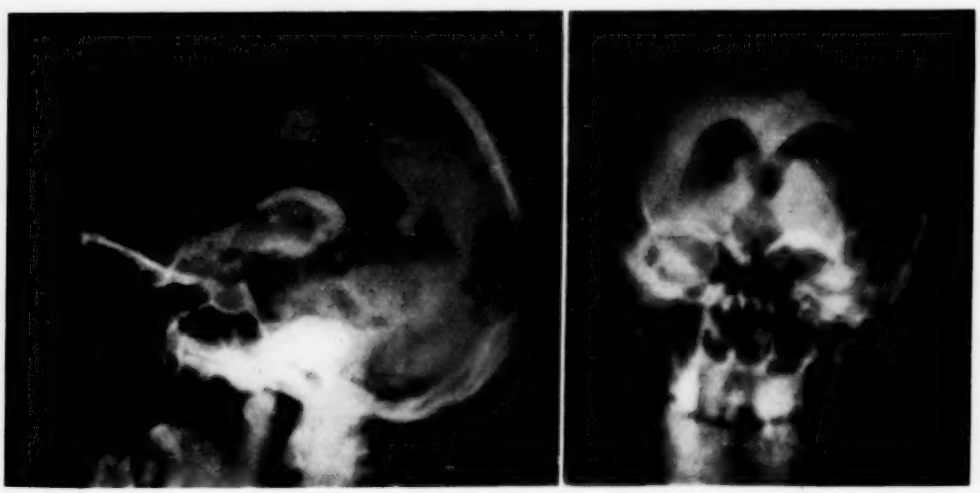

Fig. 4 *A*. Fig. 4 *B*.

FIG. 4 *A* AND *B*. Encephalogram on March 29, 1935, showing increase of internal hydrocephalus.

These medicinal agents included pituitrin (grains II, twice daily), whole pituitary gland extract, thyroid extract (grains ½, three times daily), Collip's diabetogenic pituitary extract, MacCallum-Laughton's duodenal extract, acetylcholine, and atropine. The injection of atropine, however, seemed to produce a violent attack which was difficult to control even with intravenous glucose.

The patient received two courses of non-specific foreign (typhoid vaccine) protein therapy. During the first series, which was given soon after admission, his seizures were arrested for a short period, and for this reason it was thought advisable to repeat this procedure. However, the second course of treatment had little effect on his general condition or blood sugar and did reduce the number of seizures. Blood sugar estimations before, during, and after a chill showed no changes.

Dietary measures were also discouraging. Controlled high and low carbohydrate diets with and without insulin were given a trial. The optimum conditions seemed to exist when he was allowed to eat a regular ward diet, supported at first by occasional and later by regular drinks of sweetened orange juice between meals, particularly when an oncoming attack was expected. For one month an attempt was made to induce ketosis with a ketogenic diet on the presumption that this would stimulate glycolysis; coöperation could be obtained for a high fat ketogenic diet of not more than 1:3 ratio. However, acetone was never obtained in the urine and the condition was unaffected.

As a final measure a two month course of deep roentgen-ray therapy directed to the pancreas was administered. A total of 1500 r. were directed in each of two fields without any alteration of the blood sugar or the other symptoms.

(*g*) *Discharge and Follow-Up.* The patient was discharged and transferred to the Montefiore Hospital for convalescent care on April 4, 1935. His course (to March 1936) at this institution has shown no marked changes except that his obesity has increased; the neurological picture has persisted.

Comment

The symptoms and signs in this patient were almost entirely neuropsychiatric and included changes in the central, peripheral and vegetative nervous systems as well as in the psyche. Such disturbances are characteristic of most cases of hypoglycemia. The most prominent and constant neurologic manifestations in the case were those referable to diseased striatocerebellar pathways. Throughout the period of observation the patient presented a typical Parkinsonian syndrome, which was progressive in nature, and therefore suggested a primary disease of the basal ganglia. Other significant neurologic changes included a transient attack of peripheral polyneuritis, progressive bilateral nerve deafness, emotional and intellectual deterioration, and progressive internal hydrocephalus.

The diagnosis was complicated by a number of unusual features. The clinical history was not suggestive of hypoglycemia since there was no noticeable relation between the symptoms and the intake of food; the attacks had occurred at any period during the day and despite the ingestion of meals. It is significant that the condition was considered as a neurologic problem in two hospitals. On admission, when the patient was in stupor an intravenous injection of glucose yielded no improvement. Recovery following the intravenous administration of glucose was not noted until about four months after admission. It is therefore evident why the hypoglycemia was not recognized, or even suspected on admission. A similar observation has been reported by Feiner, Soltz, and Haun [4] in a verified case of adenoma of the pancreas. This observation is difficult to explain.

The fasting venous blood sugar estimations were remarkably low as compared to other reported cases. The general level of the reducing substances varied from 30 to 45 mg. per cent, and when allowance was made for other reducing substances, the yeast fermentable sugar was estimated as low as 5 mg. per cent.

It was also found that there was no strict parallelism between the level of the blood sugar and the severity of the symptoms (figure 1). At certain times the blood sugar values were low without attacks, whereas at other times when the levels were higher convulsions were present. Too, most of the seizures occurred in the afternoons (table 1) despite the fact that the patient ate his lunch. It is possible that the ingestion of food may have overstimulated insulin formation. The ingestion of food did not prevent symptoms of hypoglycemia, a fact contrary to most reports. Most observers state that the intake of food, especially in the form of sweetened orange juice prevents or checks the hypoglycemic attack almost immediately. In our case, no method except the intravenous administration of glucose was successful. Even small amounts of glucose by this channel were effective. Glucose by mouth, by rectum or subcutaneously was without result. The effect of fever therapy in this case merits additional reference. During the first course of foreign protein therapy, the patient showed remarkable improvement and convulsive seizures did not occur. At a later period, however, the repetition of this treatment was less effective, in that the hypoglycemic attacks diminished in number but did not disappear entirely as previously. Moreover, blood sugar estimations at this time showed no change; the fasting and other sugar values were the same as on days prior to the institution of foreign protein therapy. Theoretically, if the condition of our patient may be considered as one of hyperinsulinism, the fever therapy may have been effective in reducing the activity of the endogenous insulin. The occurrence of this phenomenon is well known in febrile diabetic patients in whom it is found necessary to increase the maintenance doses of exogenous insulin.

This is probably the first case of hypoglycemia in which progressive internal hydrocephalus has been demonstrated by encephalography. The exact significance of this change must await pathological studies. Other noteworthy alterations during the hypoglycemic seizure were increased salivation, changes in the T-waves of the electrocardiogram, a decrease of blood cholesterol, and a reduction of ocular tension. The latter finding is similarly found in the quite contrary condition of diabetic coma.

The etiology of the hypoglycemia in our case is not clear. Some authors attach importance to the pituitary gland as a causative factor, but the evidence for such an hypothesis is not well established. The only endocrine disturbances manifested in our patient were increase in weight and development of greasiness of the face, and these may be due to disease in the vegetative nervous system. The obesity was probably due to an increase in the caloric intake from the sweetened orange juice given every two hours in order to avoid the hypoglycemic attacks. Diseases of the pancreas, liver and adrenals as the cause of hypoglycemia were probably excluded by exploratory laparotomy and biopsy. However, biopsy of normal tissue from one part of the pancreas or liver, or palpation of the adrenals does not necessarily exclude pathologic lesions in other parts of the explored organs. Furthermore, one may also be reminded that it is possible to have abnormal function in the presence of normal morphology. In the final analysis altered function is more significant than altered structure. Numerous instances have been cited where individuals were suffering with hypoglycemia of unknown etiology. These cases are designated as idiopathic, and in most instances the pancreas has been explored and found to be negative.

Finally in our patient, the persistence of the extrapyramidal syndrome raised the question whether the disease of the periventricular nuclei caused both the abnormal movements as well as the hypoglycemia. Theoretically it is possible that disturbances in the sugar metabolism may occur from disease of the glucose regulating center in the brain. As a matter of fact, a case of acute lethargic encephalitis associated with disturbances in sugar metabolism and vegetative functions was recently observed by us. The course, however, in this case was acute and brief, and the disturbances were transient. In the patient with "chronic hypoglycemia" the symptoms and signs of basal ganglia disease were insidious in onset and persistent. From these observations one may infer that disease of the vegetative centers may produce chronic hypoglycemia. On the other hand, one may argue that a persistent hypoglycemia, whatever the cause may be, may produce permanent damage to the brain and therefore produce manifestations of disturbed nerve function. Recent experiments performed on rabbits revealed that convulsions caused by hypoglycemia produced definite anatomic changes in the central nervous system, and the greater the number and the more prolonged the convulsions, the more severe were the lesions.[5] Our patient had numerous convulsions and encephalograms taken a few months apart revealed a progressive internal hydrocephalus. It is possible that the changes in the brain in this case were caused by the repeated convulsive seizures. On the other hand, it may be claimed that the internal hydrocephalus was the result of primary disease of the brain and that the hypoglycemia which caused the convulsions was secondary.

We are unable to conclude as to which theory is correct. In any case there seems to be a definite relation between disease of the periventricular nuclei and glucose metabolism.

Summary

1. A detailed case history of chronic hypoglycemia is described.

2. The outstanding features were a persistent Parkinsonian syndrome and evidence of a progressive internal hydrocephalus as shown by several encephalograms.

3. Attention is called to the coexistence of manifestations of chronic disease of the periventricular nuclei and the constant hypoglycemic state. The relation between these two is discussed from the standpoint of etiology, but no definite conclusions are drawn.

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UVEO-PAROTID FEVER; WITH CASE REPORT*

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UVEO-PAROTID fever, or Heerfordt's disease, is a comparatively rare affection characterized by (1) an iridocyclitis, (2) a bilateral almost painless swelling of the parotid glands, (3) a low grade chronic fever running a course of from several weeks to two or three years and subject to considerable variations, and (4) by the occurrence of irregular constitutional symptoms. The syndrome may occur at any age, but is most common in the second and third decades, and is slightly more prevalent in females.

Of frequent, though not constant, occurrence are: (1) a prodromal stage, lasting for several weeks or months, of general malaise and drowsiness with a tendency to frequent gastrointestinal upsets and abdominal pains; (2) paresthesias and polyneuritis; (3) paralysis of the cranial nerves, particularly the seventh; (4) a rash resembling erythema nodosum occurring chiefly on the extensor surfaces of the forearms and legs and extending slightly above the knees and elbows; (5) a polyarthritis; (6) swelling of the cervical lymph nodes and the submaxillary and lacrimal glands; (7) a polyuria without glycosuria; and (8) a long continued dryness of the mouth.

The eye symptoms are quite variable. They may include misty vision with more or less impairment of sight, narrowing of the palpebral fissures, ciliary congestion, sluggish and often irregular or dilated pupils with little or no response to light or accommodation, vitreous opacities, optic neuritis or atrophy, iritis, keratitis, cataract, and glaucoma.

The parotid swellings are usually bilateral and painless. They may be hard or nodular and limited to the pre-auricular area, or much more extensive, involving all of the salivary tissue. This engorgement usually lasts several weeks or months, but the glands never suppurate.

There seem to be great variations in the order of the appearance and in the severity and duration of symptoms, but the similarity in cases thus far reported unquestionably justifies the classification of a separate clinical entity.

CASE REPORT

History of Present Illness: The patient, a white female, aged 33, was seen by me at her home late in the night of February 14, 1935 for a severe headache and pain in and over the eyes. She also complained of a slight sore throat and aching of the entire body which had begun four or five days previously. The temperature was 102.5° F., and the pulse 110; otherwise the examination was essentially negative. Her suffering was apparently so intense that I administered morphine gr. ½, hypodermically, which soon gave fair relief. During the next two or three days I received reports to the effect that she was much improved, being able to keep fairly comfortable by the use of aspirin alone. On the eighteenth I was called to see her again, and found that in addition to an exacerbation of the initial symptoms, a distinct redness of the conjunctivae and a photophobia had developed. Two or three days later the patient complained of a blurred or misty vision and of not being able to distinguish objects in the room unless they were brought very close up. Also, she complained of an intense dryness and stickiness of the mouth. At this time there was noticed some degree of swelling on both sides of the face in the regions of the

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parotid glands. This swelling was not painful, but was slightly tender on pressure. The posterior cervical glands were also enlarged and slightly tender. Within the next two days there developed some edema of the upper lids, and the photophobia was more pronounced; also, the pupils were dilated and reacted very poorly to light. The temperature continued to range from 100° F. to 102° F., and the patient became quite drowsy, being disturbed at intervals with pains about the head. During the next few days the swelling of the parotids increased, the eyes became swollen completely closed, and the mental state varied from an intense drowsiness or lethargy to a wandering hallucinatory delirium. On February 23 and 24 an eruption appeared on the extremities, extending from approximately the middle of the arms and thighs down to and including the hands and feet, but most pronounced on the forearms and legs and involving chiefly the extensor surfaces. The lesions consisted of discrete, ecchymotic, subcuticular nodules, varying in size from about ¼ cm. to 1½ cm. in diameter. Two days later, or 16 days from the initial onset of symptoms, the patient was admitted to the Wesley Long Hospital.

Family History. A husband and two children, ages 12 and 6 years, are living and well. Both children, however, were sick for several days with "colds" a week or two before the onset of the patient's present acute illness. Neither of her children has had mumps, nor has there been any illness in the home since the patient's attack suggesting contagion. Six years ago her husband's sister who had active pulmonary tuberculosis visited in the home for two weeks. Otherwise the family history is negative.

Personal History. The patient sleeps fairly well; her appetite is good; there is no constipation or apparent inability to digest foods. Her maximum weight was 145 lbs. three years ago; present weight is 137 lbs. Menstruation began at the age of 15 and was regular and normal until after the second child was born six years ago. Since then it has occurred at five to seven week intervals; the flow is scant and lasts only two or three days. There have been two normal pregnancies and no miscarriages.

Past History. She had measles, mumps, whooping cough, and German measles as a child. Her tonsils were removed about 10 years ago. Eight years ago she had an operation at which the appendix and one ovary were removed and the gall-bladder drained. Six years ago, and about four or five months after the sister-in-law with tuberculosis visited in the home, the patient developed a pleurisy of the left side which lasted several weeks, but has never recurred. Moreover, she has had two roentgen-ray studies of the chest since which did not reveal evidence of tuberculosis. About two and a half years ago the patient began having headaches, chiefly occipital, and after having her glasses changed several times the headaches improved. She also complained of a general malaise, weakness, and fatigue. Shortly after this she began having attacks of stiffness in the wrists, shoulders, and neck, especially following exposure to drafts at night. Soon there developed pains in the chest and lower abdomen, and pains and stiffness in the lower part of the back, in the hips, legs, arms, and joints—especially of the wrists, hands, and ankles. Also, she was found to be running a slight fever.

On July 16, 1933, the patient called at my office complaining of swollen glands about the neck, and stated that the condition had been developing for a week. Her temperature was 102° F., the cervical lymph nodes, both anterior and posterior, were greatly enlarged, and there was slight enlargement of the epitrochlears. She was confined to bed for four weeks during which the glandular enlargement gradually diminished without suppurating, but the glands remained definitely larger than normal. Also, the temperature ranged lower, but continued to run from normal to 100° F. Undulant fever was considered, and upon inquiry it was elicited that a cow from which the family used milk had recently aborted. Blood was taken two weeks from the onset of this attack, and again one week later, for agglutination

against *Brucella;* both, however, were negative. The blood Wassermann was negative, and an intradermal tuberculin test was positive. A leukocyte count at this time was 4,500 with a normal differential. Two weeks later the patient was referred to an otolaryngologist who was unable to find any evidence of disease in the throat and sinuses. She was then referred to a dentist who found several diseased teeth which were extracted over a period of several months. The following October (1933) she was admitted to Duke Hospital (Durham) where a very complete study of her condition was made. A summary of their significant findings are as follows: Enlarged cervical and epitrochlear lymph nodes; temperature 100° F.; pulse 126; slight tenderness in the sacro-iliac joints, lower abdominal quadrants, and right adnexal region of the pelvis; a negative agglutination test for undulant fever; a positive tuberculin test; a low glucose tolerance (209 mg. per cent at 1.5 hours, and 130 mg. per cent at three hours); and a metabolic rate of minus 2 per cent. No diagnosis was made, but an impression of the presence of neurasthenia and, possibly, of a tuberculous infection of the Fallopian tubes was offered. Her course continued practically unchanged for approximately the next 18 months, or until the acute condition herein described developed in February 1935, when she was admitted to the Wesley Long Hospital.

On admission to the hospital the temperature was 101° F., pulse 100, and respirations 22. The heart, lungs, abdomen, and reflexes were apparently normal. In fact, with the exception of the symptoms above described, the physical examination was essentially negative.

Laboratory Findings. Urine: An occasional red blood cell and a few pus cells were found on one occasion; otherwise, negative. Blood: Erythrocytes, 3,420,000; hemoglobin (Sahli), 78 per cent; leukocytes, 16,500 with 82 per cent polymorphonuclears, 14 per cent small lymphocytes, 3 per cent large lymphocytes, and 1 per cent eosinophiles; blood platelets, 258,400; coagulation time, 4½ minutes; bleeding time, 1 min. 40 sec. Two blood cultures were negative after five days' incubation, and a culture of material aspirated from several of the subcutaneous nodules was contaminated. Roentgen-ray (Dr. E. D. Apple): "Stereo films were made of all sinuses. Both ethmoids show cloudiness involving all of the cells; the cell outlines, however, are not completely obscured. The sphenoids also appear slightly clouded. Both antra show evidence of thickened lining membrane; they do not contain fluid. The left frontal is very small and shallow. The right is larger, though still small. They both appear clear."

On the same day of admission Dr. Frank Sharpe saw this patient in consultation with me, and the following day I had Dr. E. Prefontaine (ophthalmologist) see her and take over the care of the head condition. A report of his findings and conclusions is as follows: "The patient was very drowsy. She complained of a marked photophobia and dimness of vision which had existed for about two weeks. There was a fullness of the neck and face similar to that present in mumps, a marked edema and redness of both upper lids, and a skin rash on the forearms and legs. Closer observation revealed the following: chemosis of the conjunctivae, generalized, but most marked on the temporal sides of the corneas; no evident pericorneal injection or corneal deposits; iris clear, but reacting sluggishly to light; and ocular movements normal in all fields. Intra-ocular examination—difficult on account of ptosis and photophobia—revealed media clear and eye grounds normal. No visual test was made. Examination of the nose and para-nasal sinuses revealed a marked bilateral edema and irritation of the nasal mucosa, and a purulent secretion in both nostrils. On transillumination both antra and frontals were moderately dark. The pharynx was dry and granular. There were hard nodular swellings in the regions of both parotids. The sublingual and submaxillary glands were apparently normal. After four days the edema of the lids began to disappear from the nasal side. Chemosis now being localized to the upper temporal region, the edematous lacrimal glands

could be definitely palpated, and, on retracting the upper lids, were visible. Conclusions: Acute ethmoiditis; acute parotitis; acute dacryoadenitis. Also, in considering the history of photophobia and dim vision which were most marked before the patient's admission to the hospital, it is most probable that some ciliary irritation or some neuro-retinitis had existed in spite of the absence of positive findings at the time of examination." Briefly, within three or four days following admission the symptoms began to abate, and after a stay of 11 days she left the hospital much improved and fairly comfortable. It was noticed, however, from the nurses' records that while in the hospital she voided from one to three times every night between 8 p.m. and 6 a.m.

Two weeks after leaving the hospital another examination by the ophthalmologist revealed that the vision had returned to normal, and that there were no synechiae or corneal deposits, or any evidence of optic neuritis or atrophy; also, the nasal condition had entirely cleared up. At this time the rash on the limbs, the swelling of the parotids, and the edema of the orbital tissues had practically disappeared, but there persisted for at least two months a very noticeable narrowing of the palpebral fissures. Also, during this time the patient ran a slight fever almost continually. It seldom rose above 100° F., and seemed to manifest no daily regularity, being highest in the morning about as often as in the afternoon or evening. In addition she suffered frequent attacks of severe abdominal pains, and the neuritis and joint and muscle pains continued to be quite annoying; moreover, the nocturia continued with a frequency of from one to five times every night. After about five months, or during the month of July, all of these symptoms began to abate, and by November had almost entirely disappeared. The fever first began to intermit daily, then at longer intervals, and later was seldom found above normal. Another examination of her chest, including a roentgen-ray study, was made at The Guilford County Tuberculosis Sanatorium on June 20, 1935, by Dr. M. D. Bonner who reported no evidence of tuberculosis. By late 1935 her weight was 137 lbs., the hemoglobin (Sahli) 76 per cent, and the cell counts normal. A number of urine examinations, including two cultures for tubercle bacilli, have been made with only normal findings. Also, another agglutination test for undulant fever was negative. It seems that in spite of this prolonged illness with fever, the patient has maintained her weight and energies remarkably well, and the blood picture has remained practically normal. Incidentally, it may be of interest to note that she became pregnant in July 1935, her last pregnancy having been more than six years before, and she denies having ever used contraceptive precautions.*

Discussion

Heerfordt,[1] whose name the disease now bears, was the first to recognize and describe this syndrome. In 1909 he reported three cases observed by him in the city hospital at Copenhagen, and discussed two others with similar symptoms from the literature,—one reported by Daireaux and Pechin in 1899, and the other by Collomb in 1903. Merrill and Oaks,[2] in reporting a case in 1931, reviewed the literature up to that date and tabulated an analysis of 29 previously recorded cases. Later Garland and Thompson [3] gave a still more comprehensive review of the subject, and, more recently, Savin [4] has presented a most excellent analysis of 66 published cases and added one of his own. Reports of at least seven others [5] have appeared since Savin's publication, making a total of approximately 74 recorded cases. It is interesting to note that most of the existing

* Since this article was submitted for publication the patient's pregnancy progressed normally to full term. The patient had a normal labor and delivery in February 1936, and in September 1936, reported herself free from fever and in good health.

reports have come from Scandinavia, Germany, and Great Britain; while only six have appeared in American literature. The condition is probably more common than is usually suspected, but is rare enough not to be readily recognized.

Etiology. The question of etiology in this disease is very much in controversy; moreover, there is a great diversity of opinion among the authors of reported cases concerning this point. Heerfordt [1] thought his cases were atypical mumps. Fuchs [6] was of the opinion that uveo-parotid fever could not be definitely separated from Mikulicz's disease, and Hamburger and Schaffer [7] thought it was a variety of the Mikulicz syndrome. Mohr [8] ascribed the lesions to syphilis. Viner,[9] Adams,[10] and MacKay [11] thought infections of the mouth were responsible for the condition. Ramsay [12] classed it as a deficiency disease. Parker [13] considered it to be an infective multiple neuritis with lesions in other tissues (parotid, uvea, skin, etc.). Schall,[14] Garland and Thompson,[3] Uhthoff,[15] Roenne,[16] Gjessing,[17] Cavara,[18] and others think the condition is caused by tuberculosis of a particularly fibrosing and noncaseating type—and there is considerable, though not altogether incontrovertible, evidence in support of this view. In fact, microscopically, the histological reactions of the tissues involved are apparently identical with those produced by tuberculosis. Moreover, McCurry [19] actually demonstrated the tubercle bacilli in biopsy sections from both parotid glands of a patient (case 2) presenting the uveo-parotid syndrome. And, of the five patients who have died, tuberculosis was demonstrated in four at autopsy; the fifth was not examined. At least, in the cases thus far reported, there has been an exceedingly high incidence of associated tuberculosis, suggesting very strongly a probable etiologic relationship. Merrill and Oaks [2] attribute this disease to a "specific virus or bacterium as yet undetermined"; while Cohen and Rabinowitz [5] think it is an infective-allergic condition caused by "an organism, as yet not isolated, which produces a low grade infection in a sensitized individual." In the opinion of the author, the weight of evidence, both from reported cases and from the clinical course and picture of the case observed, suggests very strongly that the condition is rheumatic in nature—thus, its protean manifestations.

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AMEBIC ABSCESS OF THE LIVER; REPORT OF A CASE WITHOUT PREVIOUS MANIFESTATIONS OF AMEBIASIS; OPERATION AND RECOVERY *

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VARIOUS authorities differ as to the prevalence of amebiasis in countries other than the tropical regions. It is claimed that it occurs in the temperate climate more frequently than is generally believed. Craig's [1] opinion that between 5 and 10 per cent of the American population harbor this infestation is based on his collected statistics of 49,336 persons examined, 11.6 per cent having been found positively infected. Sir Leonard Rogers,[2] quoting C. Dobell, stated that between 7 and 10 per cent of the people of North England were carriers of the *Endameba histolytica* during the Great War. In 1934 Wenrich, Stabler and Arnett,[3] of the University of Pennsylvania, examined 1,060 freshmen students at a professional school in Philadelphia and found that 4.1 per cent harbored the *Endameba histolytica.*

In Philadelphia prior to the Chicago epidemic of 1933 amebiasis was a sporadic disease. Between January 1926 and November 1935, among 232,100 admissions to the Philadelphia General Hospital, there was one proved case of amebic dysentery, admitted in September 1930 to the service of Dr. Russel Boles. At the Jefferson Hospital during the same period, among approximately 120,000

* Read before the Section on General Medicine of the College of Physicians of Philadelphia, January 27, 1936.

From the service of Dr. Samuel A. Lowenberg, Philadelphia General Hospital.

admissions, there were six cases of amebic dysentery. All followed the Chicago epidemic, three occurring in the latter part of 1933 and three in 1934. Up to November 1935 the Bureau of Health of Philadelphia [4] had recorded 43 cases of proved amebiasis all of which had likewise occurred subsequent to August 1933 when the segregation of the dysentery cases was first started.

The most frequent complication of amebiasis and amebic dysentery is abscess of the liver. It is frequently undiagnosed before death especially in temperate climates where amebic infection, until recently, was little understood and was

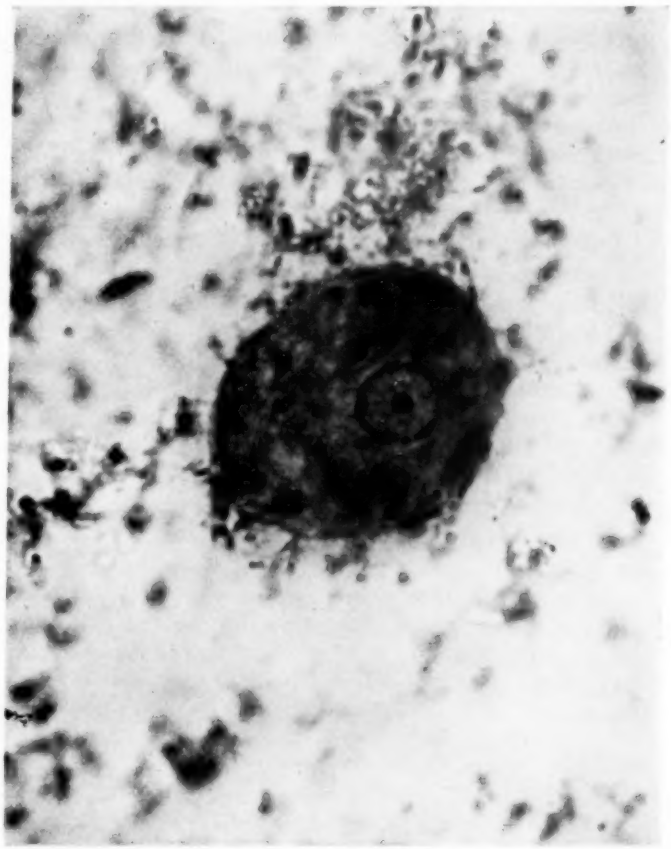

FIG. 1. *Endameba histolytica.* Vegetative form discovered in the abscess cavity. × 2024.

regarded by most of the profession as a tropical disease. Ochsner and Bakey [5] have reported on 4,484 cases of amebic abscess of the liver collected from the literature. According to some investigators amebic abscess of the liver is observed in from 2 to 20 per cent of those infected but living and in from 15 to 59 per cent of the autopsied cases of this disease. Brown [6] reported 22 cases of hepatic involvement from the records of 834 cases of amebiasis at the Mayo Clinic. Of these 16 were proved cases of hepatic abscess, approximating 2 per cent.

At the Philadelphia General Hospital during the last 10 years, among the 232,100 admissions and 24,000 autopsies, there were five cases of proved amebic abscess of the liver. Three cases were diagnosed clinically. The first was operated on by the late Dr. Hiram Loux in 1925. The second was the case which is the subject of this report, occurring in October 1935. The third was admitted later in 1935 and was operated on by Dr. Mitchel P. Warmuth. The remaining two were diagnosed at autopsy. At the Jefferson Hospital during the last 10 years there has been but one case of clinically proved amebic abscess of the liver, admitted on July 31, 1933, to the service of Dr. Henry K. Mohler and operated upon by Dr. Thomas Shallow. This was the only case recorded in this hospital although approximately 3,000 autopsies were performed within this decade. If amebiasis is, or has been, prevalent in Philadelphia either our diagnostic acumen, or our laboratory methods, or our records are at fault.

Various investigators claim that from 50 to 90 per cent of the cases of amebiasis have symptoms not usually dysenteric but mild and attributed to some other factor. It is the latent infections in the carriers of the amebic cysts that are not recognized and become potential dangers both to the host and to the community.

It must be remembered that abscess of the liver may be the first symptom of amebiasis. Ochsner and Bakey [5] claim that they have found a relatively large number of cases of amebic hepatitis without a history of diarrhea. An explanation may be that slight amebic infection of the bowel, limited to the right half of the colon is less likely to produce diarrhea. On the other hand, Strong [7] has found a history of dysentery in 60 to 90 per cent of the cases of liver abscess. Three of the four proved cases recently reported by Freund [8] failed to present any evidence of previous gastrointestinal symptoms. Rogers,[9] in 1930, reported that in 20 per cent of the cases of amebic abscess of the liver coming to autopsy in Calcutta there had been no history of dysentery. However, he found amebic ulcers, limited to the cecum and ascending colon, in 77 per cent of such cases and ulcer scars in 20 per cent more, a total of 97 per cent which yielded pathological evidence of intestinal amebiasis.

Because of the apparent rarity of amebic abscess of the liver in this climate and because of its occurrence in a patient without previous history of amebic dysentery, the report of the following case, diagnosed following operation, should be of interest.

Case Report

History: J. L., white, 58, Polish, a tanner unemployed for five years, was admitted to the Philadelphia General Hospital on September 16, 1935. Because of the language difficulty and the ignorance of the patient a good history was not obtainable. He claimed that he had been well until September 9, 1935 when he noticed a sudden onset of severe pains in the right upper abdomen, griping in character, coming on every hour or hour and one-half and lasting for 15 minutes. The pains had no relationship to food and were not associated with nausea, vomiting or diarrhea. He had persistent hiccoughing. There were no symptoms referable to the cardiac or respiratory systems. He was chilly, had fever, and felt quite drowsy.

In his past medical history he did not remember having had any childhood diseases or of having had any previous illness, hospitalization or operation. He had never been jaundiced. He had never had dysentery or blood in his stools but contrarily had been constipated. He had not traveled outside of Philadelphia. There was no history of his having come in contact with carriers.

After the operation and after a month of repeated questioning of the family we were able to procure some additional information from the patient's daughter. She stated that for a period of 15 years her father had had pains in his right upper abdomen with heartburn independent of the taking of food. There were attacks of abdominal cramps, without diarrhea, coming on twice a week and lasting 24 hours, associated with chilly sensations. These pains were relieved in one hour by taking a tablespoonful of coal oil with sugar. Upon further investigation it was learned that his son-in-law, who lived in the same house, had been treated at the Jefferson Hospital since September 1933 for a bloody diarrhea. Repeated stool examinations failed to reveal the presence of the ameba. As far as we could acertain, no other member of the household was affected.

Examination: The patient was a slightly emaciated and dehydrated adult male who appeared distressed. The conjunctivae were not icteroid. The nose, mouth and throat were negative. The heart seemed normal. The systolic blood pressure was 115 and the diastolic pressure was 85 mm. of Hg. The chest was emphysematous. The bases of the lungs were hyperresonant without any apparent fixation of the diaphragm. The abdomen revealed moderate fullness in the epigastrium over which area there were pains and tenderness which were made worse upon breathing. The upper limit of the liver dullness commenced in the fifth intercostal space anteriorly in the mid-clavicular line and extended 6 centimeters below the costal border. The lower edge of the liver could not be palpated because of the voluntary rigidity of the upper abdomen. The lower abdominal wall was relaxed. The spleen was not palpable, nor enlarged on percussion. There were no signs of fluid in the abdominal cavity. Rectal examination revealed normal sphincter control and no masses. The prostate was slightly enlarged. The examination of the skin and of the nervous systems was negative.

The temperature ranged between 100.4 and 102.1 degrees F. The pulse rate was 94 to 100 per minute and respirations were 30 per minute. The first blood count was: Hb. 14 gm.; r.b.c. 3,840,000; w.b.c. 16,000 per cu. mm. of which 96 per cent were polymorphonuclear. Of the latter 26 per cent were segmented and 70 per cent were stab forms. The lymphocytes constituted 2 per cent and the monocytes 2 per cent. There were no eosinophiles. The urine showed traces of albumin and was negative for bile. The Wassermann was negative. The urea was 10 mg. and the sugar was 90 mg. per 100 c.c. of blood. The icterus index was 10.

In the absence of a history of dysentery and because of the sudden onset of the distressing symptoms and signs suggestive of acute suppurative cholecystitis with secondary hepatitis, the patient was operated upon by Dr. Patrick McCarthy on September 18, 1935.

Upon entering the peritoneal cavity he found the gall-bladder and spleen to be normal. The left lobe of the liver was much enlarged and extended down to the umbilicus. The right lobe showed nutmeg-like surface markings and across its lower border extended a deep transverse scar about three-quarters of one inch deep which gave it the appearance of a luetic liver. Further palpation revealed another such scar running vertically and situated at the dome of the right lobe. Towards the middle of the right lobe an area protruded somewhat above the general liver surface which was bluish-gray in appearance. This area was found to be soft and fluctuant. Aspiration of the abscess yielded a thick, whitish pus. A cannula and suction drained off 10 ounces of a thick, creamy, slightly brownish pus. A 24 gauge catheter was introduced in the abscess cavity and sutured in place to the liver. The area about the liver opening was packed with iodoform gauze and the peritoneal cavity was closed.

The pus was immediately examined by Dr. Jefferson Clark who found the *Endameba histolytica.* The amebae were of large size with faintly visible nuclei and distinct refractile ectoplasm. They exhibited marked motility and contained vacuoles and occasional red blood cells. The cultures made from the pus revealed *Bacillus coli.*

Dr. R. P. Custer's examination of the liver tissue removed at the time of the operation revealed a marked chronic proliferative peri-portal hepatitis.

Two days following the operation the distressing symptoms subsided. The temperature returned to normal where it remained. The drain was removed in seven days after which the incision healed and convalescence was uneventful. The patient was able to resume a full diet.

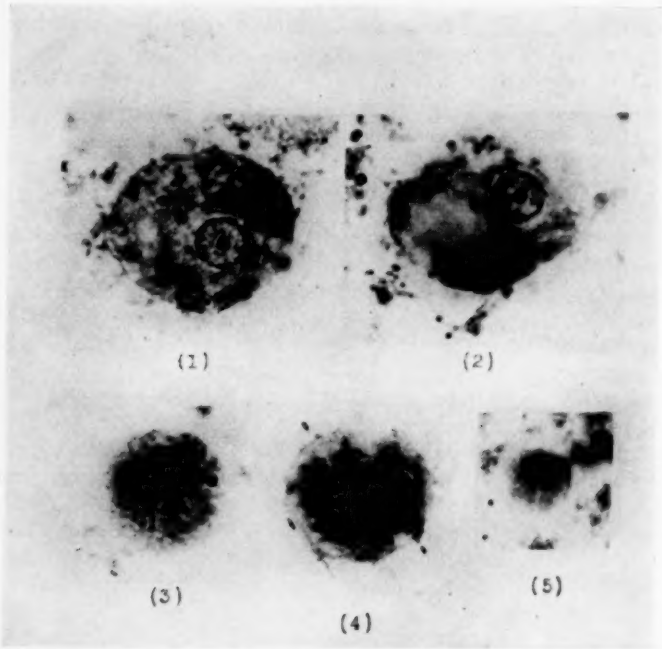

FIG. 2. (1 and 2) *Endameba histolytica.* Vegetative forms removed from the abscess cavity of the patient. For comparison (3) *Endameba histolytica.* Cyst. (4) *Endameba coli.* Vegetative form. (5) *Endameba coli.* Cyst form. × 2024.

After his return to the medical service, the first week in October, further studies were inaugurated. The bromsulphthalein test showed no retention beyond 30 minutes. The gastric analysis was normal. Ten stool examinations done while in the hospital were negative for ameba and for cysts. Duodenal drainage did not reveal the presence of the ameba. The Craig complement fixation test was not performed.

The proctoscopic examination revealed that the anus showed a fissure at the posterior commissure. There was a nest of internal hemorrhoids. The lower 10 centimeters of the bowel were normal showing no evidence of ulceration.

A roentgen-ray of the chest was normal. The diaphragm was not altered in function or position. Roentgenographic study of the colon revealed that barium passed uninterruptedly from the rectum to the cecum. There was a marked reduplication of both flexures and ptosis of the transverse colon which lay over the first sacral segment. Numerous annular radiolucent shadows were seen throughout which

were caused by intestinal gas. There was marked irregularity about the cecum but no demonstrable irritability. The appearance was suggestive of some inflammatory processes involving the cecum.

The patient was discharged as clinically relieved on November 21, 1935.

FIG. 3. Roentgen-ray of the colon. Note the marked irregularity about the outer edge of the cecum and the ascending colon suggesting an inflammatory process.

TREATMENT

Upon the patient's return to the medical ward amebicidal therapy was instituted. It is interesting to note that, because of abdominal cramps over a period of 15 years, he had been accustomed to take a tablespoonful of coal oil by mouth twice a week and had obtained relief. Kerosine has been used for amebiasis.

Every suspected or proved case of amebic abscess of the liver should be given the advantage of a course of emetine therapy before any other procedure is used unless there is an apparent surgical complication. However, Reed [10] believes

that intensive emetine treatment should be avoided before operation because of the possible harmful effect on the myocardium.

If the symptoms and signs persist after amebicidal therapy then surgery is indicated. Although there may be multiple amebic abscesses of the liver, the majority are solitary and in the right lobe of the liver, and are sterile. In Ochsner and Bakey's [5] series of 386 collected cases where smears and cultures were made from the pus of amebic abscesses of the liver, 328, or 83.9 per cent, were found to be sterile. In their own 46 cases, 41, or 89 per cent, were free from bacteria. The concensus of opinion is that closed drainage is the method of choice. It is based on the experience of Rogers [2] who has shown that the mortality rate of open drainage was as high as 56.8 per cent while in closed drainage the rate decreased to 14 per cent. In Ochsner and Bakey's [5] 4,035 collected cases, following open drainage there were 1,908 deaths, a mortality rate of 47.2 per cent. In the 459 cases treated by closed drainage and the administration of appropriate doses of emetine they found 32 deaths, or a mortality rate of 6.9 per cent.

When smears of the abscess contents examined at the time of aspiration show the presence of a large number of microörganisms, or when fluid re-accumulates in spite of repeated aspirations, and when there are indications of surgical complications, such as beginning perforation, then open drainage is to be preferred. In all other cases the concensus of opinion is that open drainage is contraindicated.

Immediately after the operation intramuscular injections of emetine hydrochloride should be given in doses of 1 grain daily, not exceeding 10 milligrams per kilogram of body weight. The average adult should not receive more than 10 grains.

Amebicides as acetarsone, carbarsone, tryparsol, chiniofon and vioform are safer and more efficient in the treatment of amebic dysentery. Leake [11] believes that they should not be used in amebic hepatitis and liver abscess because they may be toxic to the liver.

Summary

If amebiasis is present in between 5 and 10 per cent of the American population, it is of interest that the records of the Philadelphia General and Jefferson Hospitals contain so few diagnosed cases. Since the Chicago epidemic more cases are being discovered. In Philadelphia amebic liver abscess is still rare. At the Jefferson Hospital during the last decade there was one case among approximately 120,000 admissions and 3,000 autopsies. During the same period at the Philadelphia General Hospital among approximately 232,000 admissions and 24,000 autopsies there were five proved cases. Three, including this case, were discovered clinically and two at autopsy.

It must be remembered that in a high percentage of cases the first symptom of amebiasis may be an abscess of the liver, as occurred in this case. The time elapsing between the infestation and the appearance of the liver abscess may vary from a few months to many years. The symptoms and signs may simulate any surgical liver condition. There may be moderate leukocytosis but no eosinophilia. In the absence of a history of amebic dysentery the primary lesions in the majority of instances can be located in the cecum and ascending colon which

would produce no diarrhea. The roentgen-ray examination by a contrast enema will reveal the local lesions as was found in this case.

In the absence of myocarditis every suspected or proved case should receive emetine therapy before any surgical procedure. Closed drainage is the method of choice. Open drainage without irrigation is indicated when there is beginning perforation or a mixed infection or re-accumulation after repeated aspirations and emetine therapy. It is the concensus of opinion that the arsenicals and oxyquinoline groups of drugs should not be used in the presence of liver damage.

The author wishes to acknowledge due thanks to Dr. Jefferson Clark, Director of Laboratories of the Philadelphia General Hospital, for his extreme coöperation.

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EDITORIAL

SEQUELAE OF ASPHYXIA DURING NITROUS OXIDE ANESTHESIA

NITROUS oxide-oxygen anesthesia is generally considered the safest of the general anesthetics. This belief is founded on a number of statistical studies of the anesthetic deaths occurring in very large series of general anesthesias from many countries. It is no doubt correct. Nevertheless most experienced anesthetists stress the need of particular watchfulness in the administration of nitrous oxide and the necessity of experience in its use before prolonged periods of deep surgical anesthesia are attempted.

To many internists who have had occasion to watch patients through nitrous oxide-oxygen anesthesias the reputed safety of this anesthetic must seem remarkable. Figures indicating that it causes death only once in one to five million cases are scarcely credible in the face of the obvious risks entailed in the state of semi-asphyxiation evidenced by these patients. Often this incredulity is heightened by a personal memory of one or more unreported fatalities attributable to gas anesthesia. The recent appearance of a very interesting paper by Courville [1] reporting 13 cases of nervous sequelae after nitrous oxide-oxygen anesthesia will probably result—if medical history repeats itself—in numerous further reports of similar instances and perhaps temporarily in an unreasonable degree of apprehension concerning the use of this anesthetic.

In general in the cases described by Courville nitrous oxide-oxygen anesthesia was followed by prolonged coma or stupor, by delirious states, by convulsions, muscular rigidity, extensor spasms, paralyses, etc. Nine of the 13 cases died after an interval of from 40 hours to 26 days. Four recovered, two completely and two with serious residual neurologic and mental defects. Examination of the brains in the fatal cases was carried out with great thoroughness. The macroscopic changes were minimal but histo-pathological studies showed very extensive alterations chiefly in the cortex and in the lenticular nuclei. The most striking of these lesions were areas of patchy necrosis of the superficial, intermediate or deep cortical layers. Courville considers the cerebral lesions highly characteristic of the effects of cerebral anoxemia as described in experimental animals by Gildea and Cobb,[2] and others.

While it is generally conceded that nitrous oxide possesses specific narcotic properties, experience has shown that for full surgical anesthesia it is necessary to give gas oxygen mixtures which produce a definite anoxemia. The unconsciousness of deep nitrous oxide-oxygen anesthesia is in part due

[1] COURVILLE, C. B.: Asphyxia as a consequence of nitrous oxide anesthesia, Medicine, 1936, xv, 129–247.

[2] GILDEA, E. F., and COBB, S.: The effects of anemia on the cerebral cortex of the cat, Arch. Neurol. and Psychiat., 1930, xxiii, 876–903.

to the nitrous oxide and in part to asphyxiation. In the induction of anesthesia many anesthetists use pure nitrous oxide and then change rapidly to a mixture containing approximately 90 to 93 per cent nitrous oxide with 10 to 7 per cent of oxygen for the maintenance of anesthesia. It is of interest to note that Henderson [3] in discussing progressive anoxemia classified as the third stage that in which the atmosphere contains between 10 and 6 per cent of oxygen. Concerning the symptoms he states: "The subject loses the ability to perform any vigorous muscular movements. Bewilderment and loss of consciousness follow, either with fainting or in a rigid glassy-eyed coma. If revived the subject may have no recollection of this stage. . . . When the oxygen is diminished below 6 per cent, respiration consists of gasps. Convulsive movements may occur. Then the breathing stops but the heart continues to beat for 6 to 8 minutes. Then death."

It is quite apparent therefore that the oxygen percentage in the usual anesthetic mixture is quite low enough to produce definite symptoms of anoxemia and that there is a very narrow margin of safety between the usual percentage and that which would not maintain life.

The mixture inhaled is moreover only one factor in the problem of ensuring an adequate oxygen supply to the cells of the vital centers. Obstruction of the airways, inadequate respiratory movements, pulmonary lesions interfering with absorption, increased circulation time, low hemoglobin content of the blood, factors decreasing the dissociation rate of oxyhemoglobin or the intracellular utilization of oxygen and finally muscular exertion, which greatly increases the body's oxygen needs, may all bring about severe tissue anoxia even in the presence of an adequate oxygen percentage in the gas mixture inhaled. It is obvious, therefore, that the anesthetist has many things to consider in adjusting the mixture to the needs of the individual patient and in combating such impediments to the ultimate tissue use of oxygen as he can alter with the means at his disposal. As to his judgment of the efficiency of the oxygen supply he must be guided by skin and mucous membrane cyanosis, the color of shed blood, and even more importantly by such signs of cerebral asphyxia as forced expiratory movements, clonic and tonic muscular contractions and widely dilated pupils.

It seems strange that as yet we have very few observations on human beings as to the degree of oxygen unsaturation of arterial blood during nitrous oxide-oxygen anesthesia. Those published by Raginsky and Bourne [4] suggest that there are extraordinary variations in this respect within the range of uncomplicated anesthesia. These authors in a study of 14 cases found that towards the latter part of anesthesias, varying in duration from 10 to 30 minutes, the arterial blood showed oxygen unsaturation varying between 53.3 and 5.1 per cent. Since the mixture administered contained approximately 20 per cent of oxygen, instead of the more usual

[3] HENDERSON, Y., and HAGGARD, H. W.: Noxious gases, 1927, Chemical Catalogue Co., New York, p. 98.

[4] RAGINSKY, B. B., and BOURNE, W.: Cyanosis in nitrous oxide oxygen anaesthesia in man, Canadian Med. Assoc. Jr., 1934, xxx, 518–521.

7 to 10 per cent, the extreme degrees of unsaturation encountered are all the more astonishing. There is real need of more extensive investigation of this subject.

If, in a patient under nitrous oxide-oxygen anesthesia, breathing stops temporarily or there is circulatory failure, a period of intense tissue anoxia will be superimposed upon a preceding period of relative asphyxia. It is in such cases especially that cerebral damage may be sustained which will be manifested after resuscitation by the sequelae which Courville has described. In experimental animals with artificially induced cerebral anemia 2 to 15 minutes of anoxemia have been found to cause in most instances irreparable changes in the cerebral cortex and medulla.

In Courville's nine fatal cases of residual coma and convulsions following nitrous oxide-oxygen anesthesia there were six in which during the anesthesia periods of respiratory failure had occurred and in four of these six cardiac failure had also been noted.

In one of these six cases, however, the duration of the anesthesia was brief, "only a few minutes" and the period of cardiorespiratory failure lasted only 4 to 5 minutes, yet this case developed coma, convulsions, extensor rigidity and irregular breathing and died on the fourth day. Moreover, there were three fatal cases in which the period of anesthesia was neither unusually long nor marked by any striking evidences of distress. Such instances suggest a factor of individual susceptibility and this possibility is enhanced by consideration of the many instances of all varieties of severe asphyxia which recover with no apparent residual defects.

Courville's contribution to the toxicology of nitrous oxide-oxygen should arouse interest in a more careful study by modern methods of the effects of this anesthetic upon internal respiration.

REVIEWS

Clinical Heart Disease. By SAMUEL A. LEVINE, M.D., F.A.C.P., Assistant Professor of Medicine, Harvard Medical School. 445 pages; 97 illustrations. W. B. Saunders Co., Philadelphia. 1936. Price, $5.50.

This volume has been written primarily for the general practitioner. It stresses bedside and clinical observations. It is especially valuable in that it presents many useful clinical points, derived from the rich experience and accurate observations of the author, not ordinarily found in more pretentious volumes. At times the author is apt to theorize a bit, but it is clearly stated when he is so doing.

There are chapters on the important etiological types of heart disease including a better chapter on functional heart disease than the reviewer has seen in any similar book, chapters on paroxysmal rapid heart action, prognosis, and treatment. Acute cardiovascular emergencies, the clinical significance of the systolic murmur, the patient with heart disease as a surgical or obstetrical risk are discussed in chapters that are excellent and of great practical importance. Chapter XX presents in 113 pages all the practitioner needs to know about electrocardiography.

The style is pleasant and readable, to the point but not too concise. The book is highly recommended.

W. S. L., JR.

The Specificity of Serological Reactions. By KARL LANDSTEINER, M.D., The Rockefeller Institute for Medical Research, N. Y. 178 pages. Charles C. Thomas, Springfield and Baltimore. 1936. Price, $4.00.

Over the course of some years, as the result of the researches of a number of investigators, our conception of the antigen has been considerably modified, and, with this, our ideas about the specificity of the antigen-antibody reaction. A critical review of this work is, therefore, not unneeded. The present book is essentially a translation of the German edition with such alterations and additions as were found necessary to bring it up-to-date. After a short introductory chapter, devoted largely to a clarification of the meaning of specificity, there follows a discussion of the serological specificity of proteins. Next the specificity of cellular antigens is considered and then that of the various antibodies. But the very heart of the work is to be found in the last two chapters, where are presented the investigations on artificial conjugated antigens, so largely carried out by Dr. Landsteiner and his collaborators, and on the chemistry of the specific cell substances: carbohydrates and lipoids. Well organized, clear and concise, with an extensive bibliography, this book presents an excellent review of the subject. Though intended primarily for specialists in the field of immunology, it is not too technical for others who may be interested in this branch of science.

F. W. H.

The Principles and Practice of Medicine. Designed for the Use of Practitioners and Students of Medicine. Originally written by the late SIR WILLIAM OSLER, Bt., M.D., F.R.S. Twelfth Edition; Revision by THOMAS MCCRAE, M.D. XXX + 1196 pages. D. Appleton-Century Co., Inc., New York and London. 1935. Price, $8.50.

During the past 10 years, this textbook has not been seen in student hands as often as newer, but possibly less valuable works. This may be due to the infrequency of editions, the present one being only the second since 1925. It is indeed a pleasure

to examine this edition, which has been entirely reset in a type that is distinctly easier to read, as the revisor notes.

The preface states, "There are changes and additions in practically every part of the book, perhaps more especially in the discussion of diagnosis and treatment. Certain sections are new or have been materially altered." These changes have been made, however, and the new material added, without sacrificing any of the clearness, simplicity, or completeness of the old text. The original style has been preserved, as well as most of the familiar expressions, while the old and new material is blended smoothly.

It is certainly to the student's advantage to study a text whose original manuscript and subsequent revisions have been in the hands of only two persons. Some recent texts suffer, in contrast, from their multiple authorship. The present volume is striking in its uniformity of style and quality and its conservative modernness.

T. N. C.

An Index of Differential Diagnosis of Main Symptoms. By various writers; Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D., F.R.C.P. 5th Edition. xii + 1145 pages. Wm. Wood and Co., Baltimore. 1936. Price, $16.00.

This is the most recent edition of a well-known work, first published in 1912 as a companion volume to the publishers' "Index of Treatment." With "An Index of Prognosis, and End Results of Treatment," edited by P. Rendle Short (ANN. INT. MED., 1933, vii, 677–678), it makes up a three volume set, although a different style of binding prevents uniformity of appearance.

The text consists of 925 pages, in which symptoms are listed in alphabetical order. Following each symptom is a discussion of the differential diagnosis of those conditions in which it may be observed, with a fairly complete description of each disease under its most important symptom or physical sign. The index of the book (pages 927 to 1145) is very complete, and must be used if satisfactory results are to be obtained, as the general alphabetical arrangement is incomplete and not cross-indexed.

On the whole, "An Index of Differential Diagnosis" is well written, interesting in style and readable. There are a large number of differential diagnostic tables. The book is fully and beautifully illustrated, having 742 illustrations, of which 196 are colored. Many temperature charts are also included, which, with the illustrations and differential tables, should be very useful for instruction of students.

Unfortunately, as with any work of multiple authorship, there is a tendency toward unevenness of quality. For example, in the long article on jaundice (pages 395 to 416) there is no mention of hemolytic jaundice as such, the different types of hemolytic jaundice being classified under other headings. Thus, the jaundice of malaria is classified with that due to acute fevers and infections, while icterus neonatorum, acholuric jaundice (congenital hemolytic), and paroxysmal hemoglobinuria are placed under "Jaundice Due to Unclassified Causes." The Van den Bergh reaction is poorly described, and the indirect reaction and quantitative estimation of serum bilirubin are not mentioned. Jaundice from cinchophen is not described.

Among other defects are the failure to list lymphogranuloma inguinale as a cause of swelling of inguinal lymph nodes and, in the differential diagnosis of coma, the omission of methyl alcohol or methyl salicylate poisoning. In the section on edema, the effect of depletion of blood plasma protein is not mentioned. In discussing typhus fever, the statement is made that "there is no known serum test for this disease" (p. 681); nor does the Weil-Felix reaction appear in the index.

In spite of these and other faults, the work should prove a very helpful one. Most of the articles are up-to-date and comprehensive. It is almost certainly the most useful of the three "Index" volumes offered by the publisher.

T. N. C.

Human Pathology: A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University. Fourth Edition, Revised. 1013 pages; 17 × 23.5 cm. J. B. Lippincott Company, Philadelphia. 1935. Price, $10.00.

This textbook appeared in its first edition in 1926. Since that time it has been periodically reëdited and revised to reflect the continuance of productive effort and accomplishment that the last decade has brought about. The teacher and author, who sets for himself the task of compiling a textbook for students' use, has a multiple problem on his hands. The book must be clear, complete but concise, and must necessarily evaluate, judiciously, the subjects discussed. He further obligates himself, to some degree, to keep the subject matter abreast of the times. Karsner has attempted to fulfill these prerequisites.

The book is divided into two parts, 428 pages being devoted to a consideration of general pathology and 585 pages to pathologic manifestations in the various systems. This arrangement is consistent with the method of teaching pathology in the majority of medical schools. The opening chapter deals with the general phenomena of disease and leads through the more simple processes of pigmentation, degeneration and vascular disturbance to the more complicated subjects of inflammation and neoplasms. Under physical causes of disease the effects on tissue of irradiation are emphasized over previous editions because of the more widespread use of x-ray and radium in the treatment of malignant disease. There are two additions under infectious granuloma that were not present in the earlier editions. These are tularemia and lymphogranuloma inguinale. The chapter on tumors has been almost completely rewritten, without change in the classification. There are also noteworthy changes in the chapters on the hematopoietic system and ductless glands. This has necessitated minor changes in the discussions on tumors in the various systems.

There is some consideration given to the virus diseases as they affect the central nervous system, but no specific mention of lymphocytic choriomeningitis is made. The so-called Rickettsial diseases, typhus, spotted fever, tick fever, are not listed in the index. These are of especial interest in certain localities.

The outline at the beginning of each chapter is especially helpful to the student. The illustrations are well selected and for the most part original. Many are reproduced from drawings. This often exaggerates detail and adds to the clarity of the reproduction. The references are well selected, mostly in English and easily accessible in alphabetical order at the end of each chapter. There are more than 300 new references in this new fourth edition.

The book is primarily a text for students and in this it well fulfills its purpose and further it offers the average practitioner a ready and easily accessible source of information on pathology.

C. G. W.

COLLEGE NEWS NOTES

Life Membership

Some years ago the Board of Regents of the American College of Physicians, believing a sound financial foundation to be one of the best guarantees of insuring the stability and perpetuity of the College, provided for the building up of an Endowment Fund, "the principal of which shall be held intact and invested in securities approved by the Board of Regents, while the income shall be available for carrying out the purposes of the organization." This Endowment Fund has been built up primarily through Life Membership Fees, the income from which has materially helped in carrying on the work of the College, especially the promotion of scholarships, fellowships and awards, and may help materially in the furnishing of the new College Headquarters.

The Life Membership Fee, ranging from a minimum of $100.00 to a maximum of $300.00, plus the original Initiation Fee, depending upon the age of the member at the time Life Membership is taken out, entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual Sessions and to the official publications of the College, including the Directory and the Annals of Internal Medicine. They receive an appropriate Life Membership Certificate, as illustrated in the Directory of the College, and their names are added to the permanent roll of contributors to the College Endowment Fund. Life Members are *active members for life.*

The plan affords the member an opportunity of paying his full dues during his productive years, while his income is greatest, thus avoiding the burden of dues later in life. The plan is one that provides a means for underwriting dues years in advance, but of receiving the premium of active membership throughout one's entire life. A member pays no more for Life Membership than he would pay for ordinary active membership to sixty-five years of age, without active membership thereafter; yet he receives active membership not only until sixty-five, but for the balance of his life. Many members can readily afford Life Membership during their active, productive years, but, with changing conditions or ill health, find annual dues a burden in later life.

The Life Membership plan of the College is bound to be a successful one because it is two-sided: it is good for the member and it is good for the College. It protects the individual's membership for life; it establishes an Endowment Fund for the College, which must be kept intact, the income only to be used for current needs.

Dr. R. L. Leak, Superintendent of the Connecticut State Hospital, Middletown, Conn., has become a Life Member of the College under date of November 25, 1936.

College Library

With the acquisition of an appropriate headquarters for the American College of Physicians with adequate facilities for housing more appropriately the Library of books written by members of the College, there has been an impetus given to the donation of books by the authors. We are gratified to acknowledge receipt of the following gifts by the authors:

Books

Dr. Wyndham B. Blanton (Fellow), Richmond, Va.—autographed books: (1) "Medicine in Virginia in the Seventeenth Century"; (2) "Medicine in Vir-

ginia in the Eighteenth Century"; (3) "Medicine in Virginia in the Nineteenth Century";

Dr. William B. Castle (Fellow) and Dr. George R. Minot (Fellow), Boston, Mass.—1 autographed book, "Pathological Physiology and Clinical Description of the Anemias";

Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—1 copy, Eighth Supplement to "New Modern Drugs";

Dr. Samuel A. Levine (Fellow), Boston, Mass.—1 autographed book, "Clinical Heart Disease";

Dr. Robert L. Levy (Fellow), New York, N. Y.—1 book, "Diseases of the Coronary Arteries and Cardiac Pain";

Dr. Jonathan C. Meakins (Fellow), Montreal, Que.—1 book, "The Practice of Medicine";

Dr. William C. Menninger (Fellow), Topeka, Kan.—1 autographed book, "Juvenile Paresis";

Dr. Martin E. Rehfuss (Fellow), Philadelphia, Pa.—1 autographed book, "The Medical Treatment of Gall Bladder Disease";

Dr. Arthur Hawley Sanford (Fellow), Rochester, Minn.—1 book, "Clinical Diagnosis by Laboratory Methods";

Dr. W. D. Sansum (Fellow) and Dr. R. A. Hare (Fellow), Santa Barbara, Calif.—1 autographed book, "The Normal Diet and Healthful Living";

Dr. LeRoy Sante (Fellow), St. Louis, Mo.—2 books: (1) "Manual of Roentgenological Technique"; (2) "Injuries to the Bones and Joints, Roentgenologically Considered";

Dr. Torald Sollmann (Fellow), Cleveland, Ohio—1 autographed book, "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology";

Dr. J. W. Torbett (Fellow), Marlin, Tex.—a book of poems, "Centennial Songs."

Reprints

Dr. Grafton Tyler Brown (Fellow), Washington, D. C.—1 reprint;

Dr. Charles R. Castlen (Fellow), Glendale, Calif.—1 reprint;

Dr. Charles Walter Clarke (Fellow), New York, N. Y.—1 survey, "Control of Syphilis and Gonorrhea in the Scandinavian Countries and Great Britain";

Dr. A. R. Foss (Fellow), Missoula, Mont.—2 reprints;

Dr. D. Waldo Holt (Fellow), Greensboro, N. C.—1 reprint;

Dr. Herbert T. Kelly (Fellow), Philadelphia, Pa.—2 reprints;

Dr. George R. Minot (Fellow), Boston, Mass.—1 reprint;

Dr. Kenneth Phillips (Fellow), Miami, Fla.—2 reprints;

Dr. Ellen C. Potter (Fellow), Trenton, N. J.—1 reprint;

Dr. William B. Rawls (Fellow), New York, N. Y.—1 reprint;

Major James S. Simmons (Fellow), (MC), U. S. A.—2 reprints;

Dr. Walter M. Simpson (Fellow), Dayton, Ohio—3 reprints;

Dr. George E. Wakerlin (Fellow), Louisville, Ky.—2 reprints;

Dr. W. H. Watterson (Fellow), La Grange, Ill.—2 reprints;

Dr. Marcos Fernan-Nunez (Associate), Milwaukee, Wis.—1 reprint;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;

Dr. Walter E. Leonard (Associate), Hollywood, Calif.—2 reprints;

Dr. Charles B. Sanders (Associate), Dallas, Tex.—3 reprints;

Dr. Francis H. Sleeper (Associate), Worcester, Mass.—2 reprints.

The Legation of the Dominican Republic, Washington, D. C., has contributed to the Library a book, "President Trujillo—His Work and the Dominican Republic."

At the Annual Clinic Day conducted at the Memorial Hospital, Pawtucket, R. I., on November 4, 1936, the guest speakers were as follows:

Dr. John Eiman (Fellow), Assistant Professor of Pathology, Graduate School of Medicine, University of Pennsylvania, "Observations on Hypo and Hyper Chloremia";

Dr. George Morris Piersol (Fellow), Professor of Medicine, University of Pennsylvania, "Importance of Restoring and Maintaining Proper Chemical Balance in Chronic Renal Conditions";

Dr. H. L. Bockus (Fellow), Professor of Gastro-Enterology, Graduate School of Medicine, University of Pennsylvania, "Regional Ileitis and Ileo Colitis";

Dr. H. B. Wilmer (Fellow), Assistant Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, "Glucose Tolerance and Metabolism in the Allergic Individual";

Dr. William D. Stroud (Fellow), Professor of Cardiology, Graduate School of Medicine, University of Pennsylvania, "Result of Five Years' Study at Pennsylvania Hospital of Various Digitalis Preparations and the Present Attitude Towards Digitalis in the Treatment of Cardio-Vascular Disease."

At last year's clinic the guest group was headed by Dr. James H. Means (Fellow) of Boston, Mass. The chairman at these meetings is Dr. John F. Kenney (Fellow) of Pawtucket, R. I.

Dr. Thomas Parran, Jr., Surgeon General of the U. S. Public Health Service, addressed the College of Physicians of Philadelphia November 14 on "Social Diseases from the Public Health Point of View." The lecture was given under the auspices of the James M. Anders Fund, established by the late Dr. Anders (Master).

Dr. Howard M. Jamieson (Fellow), formerly of Wilkes-Barre, Pa., has been appointed Chief of the Pathological Department of the Loughborough and District General Hospital, at Loughborough, Leicestershire, England.

Dr. Porter Paisley Vinson (Fellow), formerly with the Mayo Clinic at Rochester, Minn., has accepted the appointment as Professor of Bronchoscopy, Esophagoscopy and Gastroscopy in the Medical College of Virginia. His new address is 300 Medical Arts Bldg., Richmond, Va.

Dr. George Herrmann (Fellow), Professor of Clinical Medicine in the University of Texas Medical School, conducted a clinic on "Faints and Fits or Syncopal Attacks" and presented a paper on "Some Newer Aspects of the Problems of Heart Failure" as the guest of the Section of Medicine of the Michigan State Medical Society, Detroit, on September 23, 1936.

Dr. James Alexander Miller (Fellow and Ex-President), Professor of Clinical Medicine, College of Physicians and Surgeons of Columbia University, has been elected President of the New York Academy of Medicine for a term of two years; Dr. Arthur F. Chace (Fellow) was elected Vice-President for three years.

Dr. George A. Sherman (Fellow), is now Medical Director of the Oakland County Tuberculosis Sanatorium, Pontiac, Mich.

Dr. Salvatore Lojacono (Fellow), formerly Superintendent of the Morgan Heights Sanatorium, Marquette, Mich., has joined the Staff of the Desert Sanatorium of southern Arizona, Tucson, October 1, 1936.

Dr. Max Pinner (Fellow), has now established his final and official headquarters at the Hermann M. Biggs Memorial Hospital, Ithaca, N. Y.

Dr. Charles R. Castlen (Fellow) has resumed practice, after a period of illness, at 501 Glendale Professional Bldg., Glendale, Calif. Dr. Castlen was formerly located in Seattle, Wash.

Dr. Edward E. Cornwall (Fellow) and Dr. Frank Bethel Cross (Fellow) are respectively Chairman and Secretary of the new Section on History of Medicine of the Medical Society of the County of Kings (Brooklyn, N. Y.).

Dr. Cross is also President of the recently reorganized Brooklyn Society of Internal Medicine.

Dr. Anthony Bassler (Fellow), New York, N. Y., will be the guest speaker at the New Orleans Graduate Medical Assembly, March 8 to 12, 1937. The subjects he will present are: "Hepatic Insufficiencies in Relation to Bodily Disorders" and round table talks on (*a*) "A Consideration of Diagnostic Criteria of Peptic Ulcer and Its Treatment"; (*b*) "The Dysenteries—Amebic and Bacillary"; (*c*) "Discussion on Biliary Tract Disease."

The Second Congress of the International Society of Gastroenterology will be held in Paris, France, September 13 to 15, 1937. The subjects to be discussed are "The Diagnosis of Gastric Carcinoma" and "The Acute and Chronic Occlusions of the Small Intestine." This Congress will be followed immediately by the International Congress on Hepatic Insufficiencies to be held in Vichy (ninety miles from Paris) on September 16 to 18. The United States National Committee of the International Society of Gastroenterology has been formed by representatives of the various gastroenterological societies in this country. Dr. Anthony Bassler (Fellow), New York, N. Y., Dr. Hyman I. Goldstein (Associate), Camden, N. J., Dr. A. C. Ivy (Fellow) and Dr. Lathan A. Crandall, Jr., both of Chicago, and Dr. Norman W. Elton (Reading, Pa.) compose the American group who will present the subject: "The Relation of Hepatic Insufficiency to General Nutrition and Especially to the Nervous System." Information concerning membership may be obtained from the President, Dr. Anthony Bassler, 121 East 71st Street, New York City.

The program of the Eleventh Series of Friday Afternoon Lectures at the New York Academy of Medicine discloses a number of the Fellows of the College as contributors:

November 6, 1936: "The Early Diagnosis and Treatment of Hypertensive Cardio-Vascular Disease," by Dr. W. W. Herrick (Fellow), Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University;

November 13, 1936: "The Gall Bladder Problem," by Dr. Martin E. Rehfuss (Fellow), Clinical Professor of Medicine, Jefferson Medical College;

January 15, 1937: "Recent Advances in the Treatment of Chronic Arthritis," by Dr. R. Garfield Snyder (Fellow), Chief of the Arthritis Clinic, Hospital for the Ruptured and Crippled, New York City;

January 22, 1937: "Recent Advances in the Endocrine Field," by Dr. David P. Barr (Fellow), Professor of Medicine, Washington University;
February 26, 1937: "Modern Concepts of Anemia from the Clinical Standpoint," by Dr. Edward B. Krumbhaar (Fellow), Professor of Pathology, University of Pennsylvania School of Medicine;
April 2, 1937: "The Diagnosis and Management of the Commoner Clinical Allergies," by Dr. Robert A. Cooke (Fellow), Assistant Professor of Clinical Medicine, Cornell Medical College;
April 9, 1937: "A Study of Four Hundred Cases of Pulmonary Tuberculosis," by Dr. George Foster Herben (Fellow), Physician in Chief, Loomis Sanatorium.

Dr. Guy W. Carlson (Fellow), Appleton, Wis., is President of the Outagamie County (Wisconsin) Medical Society and Secretary of the Sixth Councilor District of the Wisconsin State Medical Society.

Dr. John H. Peck (Fellow), Des Moines, Iowa, has removed to Oakdale, Iowa, where he has accepted the appointment as Superintendent of the Iowa State Sanatorium, November 1, 1936, to fill the unexpired term of Dr. J. A. Edwards, who was killed in an automobile accident during October.

Dr. J. C. Kamp (Fellow), Casper, Wyo., has just completed an extended visit to the clinics and hospitals of London and Vienna.

Dr. Alexsei Leonidoff (Associate) addressed the Dutchess Putnam Dental Society October 29 on "Diseases of the Heart and Lungs," pointing out their relations to dentistry.

Dr. Alfred R. Masten (Associate) has been appointed Director of the Division of Tuberculosis Control, Colorado State Board of Health, with offices at 424 State Office Bldg., Denver, Colo.

Dr. James B. Collip (Fellow), Professor of Biochemistry, McGill University Faculty of Medicine, Montreal, Que., received the honorary degree of doctor of science during the Tercentenary of Harvard University in September.

Dr. William Thalhimer (Fellow) is in charge of the Manhattan Convalescent Serum Laboratory, which has been established in the research laboratory of the department of health for preparation and distribution of immune serums for measles, scarlet fever and other communicable diseases.

Dr. J. Burns Amberson, Jr. (Fellow) and Dr. Edgar Mayer (Fellow), New York City, have been appointed consultants on dust diseases by the State Industrial Commissioner.

Dr. Martin L. Stevens (Fellow), Asheville, N. C., has been appointed a member of the Board of Trustees of the State Tuberculosis Sanatoria.

Dr. Paul P. McCain (Fellow), Superintendent of the State Sanatorium, Sanatorium, N. C., was the recipient of the honorary degree of doctor of laws at the annual commencement of the University of North Carolina.

Dr. Henry A. Christian (Fellow) delivered the third Frank Billings Lecture of the Thomas Lewis Gilmer Foundation of the Institute of Medicine of Chicago at a joint meeting with the Chicago Society of Internal Medicine, October 26, on "Edema, Diuretics, Diuresis."

Under the presidency of Dr. Frank H. Krusen (Associate), Rochester, Minn., The Academy of Physical Medicine held its annual meeting in Boston, October 20 to 22.

Dr. Jonathan C. Meakins (Fellow), Montreal, Que., assisted in the presentation of a symposium on integration of the medical curriculum during the forty-seventh annual meeting of the Association of American Medical Colleges, Atlanta, Ga., October 26 to 27.

Dr. Chester W. Waggoner (Fellow), Toledo, has been appointed a member of the Ohio State Medical Board.

Dr. Carl S. Mundy (Fellow) and Dr. Paul M. Holmes (Fellow) have been appointed members of the Advisory Health Board, recently created for Toledo. The Board will act in an advisory capacity on all municipal health matters and will confer with the city manager, the health commissioner and the welfare director on current health problems.

Under the Presidency of Dr. Charles M. Griffith (Fellow), Medical Director of the Veterans Administration, Washington, D. C., the forty-fourth annual meeting of the Association of Military Surgeons of the United States was held at Detroit October 29 to 31. Dr. Perceval S. Rossiter (Fellow), Surgeon General of the U. S. Navy, was installed as President for the coming year. Among Fellows contributing to the program were:

Dr. Philip B. Matz, Washington, D. C., "Diabetes Mellitus among Veterans of the World War";
Dr. Frederick G. Buesser, Detroit, "Treatment of Peptic Ulcer";
Dr. William W. Hall, (MC), U. S. Navy, "Active Immunization against Tetanus with Tetanus Toxoid."

Dr. John C. Ruddock (Fellow), Los Angeles, President of the California Heart Association, gave an illustrated lecture before the seventh annual postgraduate symposium on heart disease of the San Francisco County Medical Society, November 18 to 19.

Dr. Ernest E. Irons (Fellow), Chicago, gave a clinic on pneumonia and Dr. Fred M. Smith (Fellow), Iowa City, directed a symposium on peptic ulcer in connection with the annual clinic of the University of Iowa College of Medicine, held at Iowa City, November 12 to 14.

Dr. Edwin W. Gehring (Fellow) has resigned as Editor-in-Chief of the *Maine Medical Journal*. The Journal will be continued under the direction of its Editorial Board.

The University of North Carolina in connection with its extension division and its School of Medicine is sponsoring a graduate course of lectures in Goldsboro for physicians in the eastern section of the State. Dr. Thomas Fitz-Hugh (Fellow), Philadelphia, and Dr. Paul D. White (Fellow), Boston, were those selected to give the lectures on "Common Forms of Anemia" and "Coronary Diseases," respectively.

Dr. J. Morrison Hutcheson (Fellow), was installed as President of the Medical Society of Virginia during October.

Dr. David P. Barr (Fellow), St. Louis, will deliver the Nathan Lewis Hatfield Lecture before the College of Physicians of Philadelphia, January 6, on "Parathyroids and Their Rôle in Health and Disease." Dr. Barr will deliver an address before the New York Academy of Medicine January 22 on "Recent Advances in the Endocrine Field." Dr. Barr delivered a lecture on endocrinology at the Medical Institute of the University of Toledo, November 6, on the occasion of its third annual "Postgraduate Day."

Dr. Ralph A. Kinsella (Fellow), St. Louis, addressed the Southwestern Medical Association at its twenty-third annual meeting at El Paso, November 19 to 21, on "Career of the Heart; Differential Diagnosis of Rheumatic Fever."

Dr. Arthur C. Christie (Fellow), Washington, D. C., delivered the Silvanus Thompson Lecture before the British Institute of Radiology at Westminster, December 2.

Dr. Reginald Fitz (Fellow), Wade Professor of Medicine, Boston University School of Medicine, and Director of the Evans Memorial Hospital, has been appointed Lecturer on the History of Medicine, Harvard University Medical School, for three years. Dr. Fitz is university marshal at Harvard and was formerly Associate Professor of Medicine in the Harvard Medical School before accepting the Wade Professorship at Boston University.

Dr. Horton R. Casparis (Fellow), Professor of Pediatrics, Vanderbilt University School of Medicine, Nashville, was the guest speaker at the annual dinner of the Minnesota Public Health Association, Minneapolis, November 13.

Dr. Allen K. Krause (Fellow), Baltimore, addressed the Brooklyn Thoracic Society, October 16, on "Modern Management of Clinical Tuberculosis."

Dr. Paul P. McCain (Fellow), Medical Director and Superintendent of the North Carolina Sanatorium for the Treatment of Tuberculosis has been appointed manager of a new state sanatorium now under construction at Black Mountain, near Asheville. A unit of the new hospital will be finished by April, 1937. Dr. McCain will have charge of both institutions, with assistant managers at each.

The Philadelphia County Medical Society adopted a new plan for meetings of its branch societies by arranging a symposium on the diagnosis of syphilis, the symposium being presented in turn before each branch. The speakers were:

Dr. Jefferson H. Clark (Fellow), laboratory aspects;
Dr. Sigmund S. Greenbaum (Fellow), lesions of the skin and mucous membranes;
Dr. William Egbert Robertson (Fellow), cardiovascular syphilis;
Dr. Michael A. Burns (Fellow), syphilis of the nervous system.

Dr. James E. Paullin (Fellow), Atlanta, was elected President of the American Clinical and Climatological Association at its annual meeting in Richmond, Va., October 26 to 28.

On the program appeared Dr. Howard F. Root (Fellow), Boston, "Insulin Protaminate in Treatment of Diabetes"; Dr. Frederic M. Hanes (Fellow), Durham, N. C., "Metabolic Studies in Sprue"; Dr. Edgar Mayer (Fellow), New York City, "The Dietary Treatment of Tuberculosis—More Recent Aspects"; Dr. Lewis J. Moorman (Fellow), Oklahoma City, "Calcification of the Spleen"; Dr. Roy R. Snowden (Fellow), Pittsburgh, "Treatment of the Thyroid Crisis."

Dr. Edward J. Murray (Fellow), Lexington, Ky., has been chosen President of the Southern Tuberculosis Conference.

Dr. Roland N. Klemmer (Fellow), Lancaster, Pa., was recently elected as Chief of the Medical Department of the Lancaster General Hospital.

DR. H. F. STOLL

OBITUARIES

DR. HENRY FARNUM STOLL

Henry Farnum Stoll, M.D. (Fellow and College Governor for Connecticut), Hartford, Connecticut, died September 28, 1936.

Dr. Stoll was born in Port Jervis, New York, May 25, 1878, the son of Albert and Elizabeth Farnum Stoll. He received his preliminary education in the public schools of Port Jervis, attended Cornell for two years and then took his medical training at Columbia University, College of Physicians and Surgeons, from which he graduated in 1902.

Following his graduation, Dr. Stoll served an internship at the Hartford Hospital and then began the practice of medicine in Hartford, Connecticut. His professional career was devoted to internal medicine, to the literature of which he contributed fifty-nine articles. His contributions on the subject of tuberculosis are outstanding, numbering twenty-five.

In 1905 Dr. Stoll became Assistant Physician to the Hartford Hospital, Assistant Visiting Physician in 1910 and Visiting Physician from 1923 until his death. He also held numerous hospital appointments throughout Connecticut as Consulting Physician.

During the World War Dr. Stoll served in the Medical Corps of the Army as Captain and Major, being assigned as Instructor in the Diagnosis of Tuberculosis, Army Medical School, Washington, D. C.

Dr. Stoll became a Fellow of the American College of Physicians on April 8, 1929 and Governor for Connecticut in 1930. The College meant a great deal to Dr. Stoll and its welfare interested him deeply. He was a member of numerous other medical societies, local, state and national, and a past president of the Hartford County Medical Society.

On September 19, 1911, Dr. Stoll married Miss Eleanor Roberts who, with his daughter, Miss Hortense Stoll, survives him.

Dr. Stoll was an energetic, arduous worker and student. His devotion to Medicine, his eagerness in the search for better methods of diagnosis and treatment, and his wise counsel long made him an outstanding medical consultant in Connecticut. Possessed too of a delightful sense of humor he was a most genial friend and companion.

With the passing of Dr. Stoll, another great physician has been taken from us. Of him one of his own patients has well said, "Though his presence will be keenly missed, the memory of his indomitable spirit will endure through the years and be a source of strength to those who were fortunate enough to be numbered among his friends."

OTTO G. WIEDMAN, M.D., F.A.C.P.

DR. ROBERT SPEAR

Dr. Robert Spear (Fellow), East Chicago, Ind., died August 23, 1936; aged 68 years. He was a native of Cobourg, Ont. He graduated from the Faculty of Medicine of Trinity University, Toronto, Ont., in 1897.

He served with the U. S. Army in the World War, was a former member of the East Chicago School Board, and had been a member of the Staff of St. Catherine's Hospital in East Chicago since the opening of the institution in 1929. He had practiced in this vicinity since 1897.

Dr. Spear was a member of the Lake County Medical Society, the Indiana State Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1925.

DR. GORDON LEE HASTINGS

Dr. Gordon Lee Hastings (Fellow), Little Rock, Ark., died September 14, 1936, at the age of 39. For the last three years he had served as Assistant State Health Officer and Director of Rural Sanitation of the Arkansas State Board of Health. He was a native of Virginia and was a graduate of Randolph Macon. His professional degree was conferred by the Medical College of Virginia. After serving an internship at the Stuart Circle Hospital in Richmond, he took postgraduate work at the Rockefeller Training Station at Indianola, Mississippi. In 1929, he came to Arkansas where he made an enviable record in public health work. He obtained a M.P.H. degree in 1935 from the Harvard School of Public Health.

Shortly before his untimely death, Dr. Hastings had been elected to the Assistant Professorship in the Department of Public Health Instruction of the University of Michigan. He was at his parental home visiting prior to taking up his new duties when he was suddenly stricken with an acute cardiac failure. He was married and had one son.

Dr. Hastings was elected a Fellow of the American College of Physicians in 1934. He was also a member of the Pulaski County Medical Society, the Arkansas State Medical Association, the Southern and the American Medical Associations.

Not of the aggressive type but on the contrary, modest and unassuming, Dr. Hastings nevertheless was an outstanding physician in his chosen field. His loss will be mourned not only by his family but by his former confrères and a host of friends.

OLIVER C. MELSON, M.D., F.A.C.P.,
Governor for Arkansas.

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